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THE EVOLUTION OF RHEUMATIC HEART DISEASE IN CHILDREN
FIVE-YEAR REPORT OF A CO-OPERATIVE CLINICAL TRIAL OF ACTH, CORTISONE AND ASPIRIN

*A joint report by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association.**

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THE UNITED Kingdom and United States co-operative clinical trial was set up in 1951-52 to compare the relative merits of adrenocorticotrophic hormone (ACTH), cortisone and aspirin in the treatment of rheumatic fever and the prevention of rheumatic heart disease. Over a period of approximately a year and a half, and under closely defined diagnostic criteria, 497 children under the age of 16 were admitted to the trial in 12 centres in the United Kingdom, the United States and Canada. These patients were allocated at random to one or another of the three treatments under investigation. They were treated according to a specified plan for 6 weeks and, after a further 3 weeks of detailed observation, were followed up at defined intervals. Full details of the plan of the study have been given in an earlier publication.[1]

The previous report compared the three treatment groups in detail throughout the 6 weeks of treatment, 3 succeeding weeks of observation

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This co-operative clinical trial was first proposed by Dr. John R. Mote, then assistant general manager of the Armour Laboratories. For the planning of the study, funds were provided by Armour Laboratories and Merck & Company, and space and services by the Helen Hay Whitney Foundation.

In the planning and conduct of this trial much is owed to the wise advice and guidance of the late Dr. T. Duckett Jones and the late Sir James Spence.

TABLE I.--NUMBER OF PATIENTS TRACED AT FIVE YEARS ACCORDING TO CARDIAC GROUP—U.K., U.S.A., AND U.K. AND U.S.A.

Cardiac group at start of treatment	Number of patients: At start of treatment	Died	Alive and heart status known	Alive but heart status unknown	Untraced	% Untraced
U.K.						
Group A—no or questionable carditis; no pre-existing heart disease	41	0	37	0	4	9.8
Group B—carditis present; no pre-existing heart disease	123	4*	109	4	6	4.9
Group C—with definite or questionable pre-existing heart disease	76	7†	61	3	5	6.6
All groups	240	11	207	7	15	6.2
U.S.A.						
Group A—no or questionable carditis; no pre-existing heart disease	76	0	66	4	6	7.9
Group B—carditis present; no pre-existing heart disease	129	1	112	6	10	7.8
Group C—with definite or questionable pre-existing heart disease	52	4	41	2	5	9.6
All groups	257	5	219	12	21	8.2
U.K. and U.S.A.						
Group A—no or questionable carditis; no pre-existing heart disease	117	0	103	4	10	8.5
Group B—carditis present; no pre-existing heart disease	252	5*	221	10	16	6.3
Group C—with definite or questionable pre-existing heart disease	128	11†	102	5	10	7.8
All groups	497	16	426	19	36	7.2

*1 death from acute nephritis and uræmia
†1 death from acute intestinal obstruction

and at the end of a further year of follow-up. It was concluded that there was no evidence that any of the three agents resulted in uniform termination of the disease and on all treatments some patients developed fresh manifestations during treatment. Treatment with either of the hormones had resulted in more prompt control of certain acute manifestations but this more rapid disappearance was balanced by a greater tendency for the acute manifestations to reappear for a limited period upon cessation of treatment. Treatment with the hormones was followed by a more rapid disappearance of nodules and soft apical systolic murmurs. At the end of one year, however, there was no significant difference between the three treatment groups in the status of the heart.

This second joint report records the state of the patients after a follow-up of 5 years. It is concerned with a comparison of the amount and severity of rheumatic heart disease in each of the three treatment groups at the end of this time period. It also demonstrates that the status of the heart at the start of treatment is the major factor determining the condition of the heart at the end of 5 years and that no treatment can be properly evaluated if this factor is not taken closely into account.

THE NUMBERS INVOLVED

Of the 497 cases admitted to the trial (240 U.K. and 257 U.S.*), 445 (89.5%) were known to be alive at the end of the 5 years and the status of the heart had been recorded for all but 19 of them. Sixteen (3.2%) were known to have died. Thus 92.7% of 497 cases had been traced at 5 years. Of the remaining 36 untraced patients, 9 were known to be alive at the end of 4 years, 9 at the end of 3 years, 8 at the end of 2 years, 1 at the end of one year, and 9 were lost before the end of the first year.

The numbers of deaths and the numbers successfully followed up are given in more detail in Table I. The cases have been divided into three groups according to the status of the heart on admission to the trial, namely Group A, no or questionable carditis and no pre-existing heart disease; Group B, carditis present but no pre-existing heart disease; and Group C, definite or questionable pre-existing heart disease.*

At the end of 5 years the fact of death or the status of the heart among the survivors had been recorded in 88% in Group A, 90% in Group B

*One Canadian centre took part in the trial, but for easy reference the term "U.S." is used to include all North American centres.

*The diagnostic criteria for admission to the study specified carditis as shown by any one of the following:
(a) Development of an organic apical systolic murmur or an aortic diastolic murmur under acceptable observation.
(b) Change of heart size of more than 15% on standard x-ray film by any standard method of measurement.
(c) Pericarditis revealed by a definite friction rub or by pericardial effusion.
(d) Congestive failure, in a patient under 25 years and in the absence of other causes, and shown by one or more of the following: (1) dyspnœa, (2) orthopnœa, (3) enlargement of the liver, (4) basal pulmonary rales, (5) increased jugular venous pressure or (6) œdema.
In the assessment of carditis as a criterion for entry to the trial, it was assumed in patients with no known pre-existing rheumatic heart disease or history of an attack of acute rheumatic fever, that previous to the current illness the patient's heart was of normal size and that there were no rheumatic murmurs. In other patients, observations of changes in heart size and murmurs were used in determining carditis and recorded.

and 88% in Group C. Similarly, the figures for the three treatment groups were 91% ACTH, 89% cortisone and 87% aspirin. The corresponding figure was 91% for the U.K. and 87% for the U.S.

It is clear that within these classifications no differential losses, which might obscure comparisons, have taken place.

DEATHS

Of the 497 children under the age of 16 who were admitted to the study and completed the prescribed course of treatment only 14 had died from rheumatic fever or rheumatic heart disease by the end of the 5 years of follow-up.* One of these deaths occurred shortly after the end of treatment and 4 more within the first year of follow-up. There were no deaths in the second year and only 1 in the third, followed by 4 deaths in the fourth year and 4 in the fifth. In addition there were 2 deaths from unrelated causes, namely one in the ACTH group from acute nephritis and uræmia in the fourth year, and one in the cortisone group from acute intestinal obstruction in the fourth year.

Division by treatment of the 14 deaths due to rheumatic fever or rheumatic heart disease shows 7 among the 162 treated with ACTH (4.3%), 2 among the 167 treated with cortisone (1.2%), and 5 among the 168 treated with aspirin (3.0%). Division by cardiac status at the start of treatment (Tables I and IX) shows no deaths at all in the 117 Group A cases (cases with no or questionable carditis and without pre-existing heart disease), 4 deaths (1.6%) among the 252 Group B cases (carditis present but no pre-existing heart disease), and 10 (7.8%) among the 128 Group C cases (with pre-existing heart disease). Of the Group B cases there was 1 death among the 37 patients with failure and/or pericarditis at entry (2.7%) and there were 3 deaths in the remaining 215 (1.4%) in whom these features were absent. Six of the 10 deaths in Group C were in a small group of 31 where there was already failure and/or pericarditis at the start of treatment. In other words, 1 out of every 5 of these died compared with 1 in 25 in the remainder of Group C.

There were more deaths among females (9 in 238, or 3.8%) than among males (5 in 259, or 1.9%) but the difference might very easily be due to chance. There were also more deaths among those whose disease was six weeks or more in duration when treatment was started than among those treated within six weeks of onset (8 of 104, or 7.7%, compared with 6 of 393, or 1.5%). The difference was entirely in the Group C cases where the death rate was 17.5% among patients treated late as compared with 3.4% in patients treated early (7 of 40 and 3 of 88 cases). In Group B the rates for late and early treatment were 1.9% and 1.5% respectively (1 of 54 and 3 of 198 cases). The death rate was not significantly lower among those treated within two weeks of onset (3 of 255, or 1.2%) than among those treated at 2 to 6 weeks (3 of 138, or 2.2%).

One of the most remarkable features of this study is the very low case fatality in comparison with previous reports.[2-5] In addition to the modern treatment of the disease there may, however, be a number of other factors concerned in this striking decrease in the severity of the disease. These factors could include a change in the natural history of rheumatic fever or streptococcal infection, the introduction of penicillin and sulphadiazine prophylaxis, and environmental features associated with the higher standard of living. There were also six severely ill patients reported in the U.S.A. who were kept out of the trial of randomized treatments in addition to the one who died after twenty hours of treatment (see footnote). On the other hand, not included in this study are patients with rheumatic fever too mild to be admitted to the study hospitals, a number of which limit their admissions to rheumatic fever and receive referrals from other hospitals. In other words, the case fatality rate could have been biased in either direction by these selective factors.

RECURRENCES

The study plan specified that all patients should receive daily prophylaxis with sulphadiazine, after initial eradication of the streptococcus by a 10-day course of penicillin. In spite of this schedule, there were recurrences which, for analytical purposes, were defined as the appearance, after an interval of at least 3 months' freedom from rheumatic activity, of manifestations that would have originally qualified the patient for admission to the trial. An analysis was made of all case reports in which there was retreatment for such a recurrence. There were, in total, 64 such retreated recurrences in the 5 years among 56 different cases of the 497 admitted (11%). In addition there were 16 retreated recurrences among 14 cases in which chorea was the only manifestation in the recurrence.

It is more informative, however, to limit attention to the cardiac groups A and B, since many patients in Group C had continuous rheumatic activity which made recurrence impossible to identify. In groups A and B there were, excluding recurrences of pure chorea, 42 recurrences in 36 cases (10% of the 369 cases). Further, in these two groups the 42 recurrences and 36 cases in which they occurred were divided almost exactly among the three treatment groups. Thus, there were 16 recurrences in 12 of the 114 treated by ACTH, 12 recurrences in 12 of the 128 treated by cortisone and 14 recurrences in 12 of the 127 treated by aspirin. It is clear that the frequency of retreated recurrence

*One child given cortisone who died 20 hours after the start of treatment is not included in the 497 children or the 14 deaths. With this single exception all the patients survived the course of treatment. The death rates following these courses can therefore be compared without the introduction of any bias due to the incidence of deaths during treatment.

does not bias the subsequent comparisons of the treatments used in this study.

COMPARISON OF THE TREATMENTS

The dosage schedules of ACTH, cortisone and aspirin were based on published studies and unpublished reports at that time (1950), the aim being to select a dosage likely to be effective over a period of administration short enough to indicate whether the acute attack had been differentially shortened by any one of the three drugs.

TABLE II.—NUMBER OF PATIENTS FOLLOWED UP FOR 5 YEARS AND PROPORTION WITH ONE OR MORE MURMURS AT THAT TIME, ACCORDING TO TREATMENT GIVEN AND INITIAL CARDIAC STATUS—U.K. AND U.S.A.

	ACTH			*Cortisone*			*Aspirin*		
Cardiac group at start of treatment	*No. of cases*	*With murmurs at 5 years*		*No. of cases*	*With murmurs at 5 years*		*No. of cases*	*With murmurs at 5 years*	
		No.	*%*		*No.*	*%*		*No.*	*%*
Group A—no or questionable carditis; no pre-existing heart disease	37	6	*16*	33	1	*3*	33	1	*3*
Group B—carditis present; no pre-existing heart disease									
(1) Apical systolic murmur grade I, only	5	0	*0*	19	3	*16*	15	4	*27*
(2) Apical systolic murmur grade II or III, only	18	4	*22*	17	7	*41*	25	8	*32*
(3) Apical systolic *and* apical mid-diastolic murmurs	12	9	*75*	15	6	*40*	17	8	*47*
(4) Basal diastolic murmur only	3	2	*67*	5	1	*20*	3	0	*0*
(5) Basal diastolic *and* other murmurs	16	9	*56*	9	4	*44*	9	5	*56*
(6) With failure and/or pericarditis	13	11	*85*	13	8	*62*	7	4	*57*
Group C—with definite or questionable pre-existing heart disease									
(1) Without failure and/or pericarditis	26	17	*65*	27	21	*78*	27	18	*67*
(2) With failure and/or pericarditis	10	10	*100*	7	7	*100*	5	5	*100*

The schedules were as follows:*

ACTH: U.K. patients. A daily dosage in U.S.P. units of 80 for the first 4 days, 60 for the next 3 days, 40 for the second and third weeks, 30 for the fourth and fifth weeks, and 20 for the sixth week.

U.S. patients. 120 U.S.P. units for the first 4 days, 100 for the next 3 days, 80 for the second week, 60 for the third week, 40 for the fourth and fifth weeks, and 20 for the sixth week.

Cortisone: A daily dosage of 300 mg. for the first day, 200 mg. for the next 4 days, 100 mg. for the second and third weeks, 75 mg. for the fourth and fifth weeks, and 50 mg. for the sixth week.

Aspirin: A daily dosage of 60 mg. per lb. of body weight or 10 g. (whichever was less) for the first 2 days, 40 mg. per lb. or 10 g. (whichever was less) for the next 5 days, and 30 mg. per lb. for the second to sixth weeks.

If retreatment was necessary at any time during the three months following the original course of therapy, a four-week retreatment scheme was followed using the same drug and dosage as in the first four weeks of initial therapy. No patient was retreated unless he demonstrated rheumatic activity sufficient to have brought him into the study initially. If, after three months without activity, the patient developed a new attack of rheumatic fever, he was treated as in the original course, i.e. for six weeks on the same drug and dosage, followed by a three-week period of observation.

The results among cases followed up for five years are analyzed in terms of the cardiac groups already defined.

Looking first at Group A (Table II), it will be seen that 6 of the 37 patients treated by ACTH had a murmur at the end of 5 years (all were grade I apical systolic murmurs), 1 of the 33 treated by cortisone (a basal diastolic murmur) and 1 of the 33 treated by aspirin (a grade I apical systolic murmur). The small excess in the ACTH group is not statistically significant. The striking fact which emerges from this comparison is the exceedingly small proportion of Group A cases treated at these dosage levels of ACTH, cortisone and aspirin, in which there is evidence of heart disease at the end of 5 years of follow-up. The prognosis in patients without carditis, but otherwise meeting the criteria for the diagnosis of rheumatic fever, is so good that it would be unreasonable to expect that large-dose cortisone therapy could significantly improve it. The well-recognized, occasional, severe toxic manifestations in large-dose cortisone therapy also militate against its use in such cases.[6]

In Group B (Table II), the cases are divided into 6 subgroups according to the cardiac status, ranging from the mildest of only a grade I apical systolic murmur* to the most severe of pericarditis

*Further details of the treatment schedule, including control of auxiliary therapy, can be found in the original report.[1]

*In this study, the following grades were adopted for reporting apical systolic murmurs:

Grade O — No murmur, or a murmur considered to be "functional" on the basis of its apparent origin at the pulmonic area or along the left sternal border.

Grade P — Murmur apparently localized to the apical area, but so faint as not to be transmitted to or toward the axilla. The "P" murmurs were not considered indicative of carditis.

Grade I — Soft apical systolic murmur transmitted to or toward the axilla.

Grade II — Louder similar murmur.

Grade III — Very loud similar murmur, usually transmitted to the back.

and/or failure. Examination of these groups shows no consistent difference in favour of any one treatment, but the number of cases in each group is small. Direct comparison of the effects of treatment among the total cases in Group B is not valid because of the unequal distribution of cases of different degrees of clinical severity among the three treatment groups. For example, there were more severely ill cases in the ACTH group and more of the milder cases in the cortisone group. There were only 5 ACTH in comparison with 19 cortisone cases in the group of mild cases which had only a grade I apical systolic murmur. On the other hand, there were 16 cases in which there were a basal diastolic and one or more other murmurs in the ACTH group compared with only 9 in the cortisone group. Also, there were only 7 cases of pericarditis and/or failure in the aspirin group in comparison with 13 in the group receiving ACTH and 13 in the cortisone-treated group.

ment and those with two or more murmurs at that time (Table III). Among patients who had a single murmur at start of treatment, 23% of those receiving ACTH, 27% receiving cortisone and 28% receiving aspirin still had one or more murmurs at 5 years, a negligible difference between the treatments. For those who initially had 2 or more murmurs, the corresponding proportions were ACTH 64%, cortisone 42% and aspirin 50%. For cases with failure and/or pericarditis at start of treatment the proportions were 85% for ACTH, 62% for cortisone and 57% for aspirin. In short, in the Group B cases there is no pattern in these results to indicate any advantage for one or another of the forms of treatment.

Finally, of the Group C patients without failure and/or pericarditis at the start of treatment (Table II) there were 26 receiving ACTH, 27 receiving cortisone and 27 receiving aspirin. At 5 years, 17 (65%), 21 (78%) and 18 (67%) had murmurs.

TABLE III.—CARDIAC GROUP B (CARDITIS PRESENT; NO PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS FOLLOWED UP FOR 5 YEARS AND PROPORTION WITH ONE OR MORE MURMURS AT THAT TIME, ACCORDING TO TREATMENT GIVEN AND INITIAL CARDIAC STATUS—U.K. AND U.S.A.

	ACTH			*Cortisone*			*Aspirin*		
Cardiac subgroup at start of treatment	*No. of cases*	*With murmurs at 5 years*		*No. of cases*	*With murmurs at 5 years*		*No. of cases*	*With murmurs at 5 years*	
		No.	*%*		*No.*	*%*		*No.*	*%*
Group B—carditis present; no pre-existing heart disease									
(1) One murmur, any grade	26	6	*23*	41	11	*27*	43	12	*28*
(2) Two or more murmurs, any grade	28	18	*64*	24	10	*42*	26	13	*50*
(3) With failure and/or pericarditis	13	11	*85*	13	8	*62*	7	4	*57*

It is possible, however, to allow for this unequal distribution of cases of varying degrees of clinical severity among the 3 treatment groups and thus make a valid evaluation of treatment within the entire Group B. Assuming that in each of the cardiac subgroups the three treatments had no differential effects whatsoever, we can calculate the expected outcome in group B cases for each of the three treatment groups.* The expected figures may then be compared with those which actually occurred. Thus, for ACTH the expected number of cases having murmurs at 5 years was 31 as compared with 35 observed, for cortisone 31 expected versus 29 observed, and for aspirin 30 expected and 29 observed. There is no evidence in this comparison that the prognosis has been affected more by one treatment than by another.

An alternative analysis of this important Group B can also be made by comparing separately all cases with a single murmur at the start of treatment and those with two or more murmurs at that time (Table III). Among patients who had a single murmur at start of treatment, 23% of those receiving ACTH, 27% receiving cortisone and 28% receiving aspirin still had one or more murmurs at 5 years, a negligible difference between the treatments. For those who initially had 2 or more murmurs, the corresponding proportions were ACTH 64%, cortisone 42% and aspirin 50%. For cases with failure and/or pericarditis at start of treatment the proportions were 85% for ACTH, 62% for cortisone and 57% for aspirin. In short, in the Group B cases there is no pattern in these results to indicate any advantage for one or another of the forms of treatment.

Finally, of the Group C patients without failure and/or pericarditis at the start of treatment (Table II) there were 26 receiving ACTH, 27 receiving cortisone and 27 receiving aspirin. At 5 years, 17 (65%), 21 (78%) and 18 (67%) had murmurs.

Of the 22 patients in Group C with failure and/or pericarditis 10 were treated by ACTH, 7 by cortisone and 5 by aspirin. In every one, murmurs were present at 5 years. There is once again no evidence of any significant difference between the three treatment groups.

THE EVOLUTION OF RHEUMATIC HEART DISEASE

Since there is no evidence that the treatments varied in their effectiveness, the three groups can be added together for the study of the evolution of rheumatic heart disease in this particular series of patients. The essential division is the cardiac status when treatment was begun.

CARDIAC GROUP A

Of the 103 cases in this group, 12 (12%) had a murmur at 1 year. At 5 years* (Table IV) the figure was 8, or 8% (7 with a grade I apical systolic murmur and 1 with a basal diastolic murmur). It appears that the outlook is better for the 71 patients without any murmur than for the 32 with

*The proportions with murmurs at 5 years were taken separately for the U.S.A. and the U.K. for each of 6 subgroups in Group B *for all 3 treatments combined.* These proportions were applied to the actual number of patients *on each treatment* and in each of the 6 subgroups (U.S.A. and U.K. separately) to see how many in the small subgroups would have had a murmur at 5 years if they had experienced the total rate of occurrence. The "expected" numbers in each small subgroup were then added to give the total number of Group B cases expected to have murmurs. The numbers expected can then be compared with the observed numbers of cases with murmurs at five years.

*Murmurs in all cardiac groups both appeared and disappeared in the time interval between 1 and 5 years. Thus in some cases murmurs present at 1 year were absent at 5 years, while in other cases without murmurs at 1 year a murmur was present at 5 years.

TABLE IV.—CARDIAC GROUP A (NO OR QUESTIONABLE CARDITIS; NO PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS FOLLOWED UP FOR 5 YEARS AND PROPORTION WITH ONE OR MORE MURMURS AT THAT TIME—U.K., U.S.A., U.K. AND U.S.A.

	U.K.			*U.S.A.*			*U.K. and U.S.A.*		
Cardiac subgroup at start of treatment	*No. of cases*	*With murmurs at 5 years*		*No. of cases*	*With murmurs at 5 years*		*No. of cases*	*With murmurs at 5 years*	
		No.	*%*		*No.*	*%*		*No.*	*%*
Group A—no or questionable carditis; no pre-existing heart disease	37	6	*16*	66	2	*3*	103	8	*8*
No murmur	30	3	*10*	41	0	*0*	71	3	*4*
Questionable murmur*	7	3	*43*	25	2	*8*	32	5	*16*

*A murmur apparently localized to the apical area but so faint as not to be transmitted to or toward the axilla.

a questionable murmur* at the start of treatment, 96% with no apparent heart disease compared with 84%. The difference is not formally significant but it appears in both countries and is in accordance, as shown later, with the general trend of the results.

The number of retreated recurrences in Group A was 10, but none of the nine patients followed up for 5 years had a murmur at that time.

TABLE V.—CARDIAC GROUP B (CARDITIS PRESENT; NO PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS FOLLOWED UP FOR 5 YEARS AND PROPORTION WITH ONE OR MORE MURMURS AT THAT TIME—U.K., U.S.A., AND U.K. AND U.S.A.

	U.K.			*U.S.A.*			*U.K. and U.S.A.*		
Cardiac subgroup at start of treatment	*No. of cases*	*With murmurs at 5 years*		*No. of cases*	*With murmurs at 5 years*		*No. of cases*	*With murmurs at 5 years*	
		No.	*%*		*No.*	*%*		*No.*	*%*
Without failure and/or pericarditis	97	36	*37*	91	34	*37*	188	70	*37*
(1) Apical systolic murmur grade I, only	14	4	*29*	25	3	*12*	39	7	*18*
(2) Apical systolic murmur grade II or III, only	28	10	*36*	32	9	*28*	60	19	*32*
(3) Apical systolic *and* apical mid-diastolic murmurs	24	11	*46*	20	12	*60*	44	23	*52*
(4) Basal diastolic murmur only	6	1	*17*	5	2	*40*	11	3	*27*
(5) Basal diastolic *and* other murmurs	25	10	*40*	9	8	*89*	34	18	*53*
With failure and/or pericarditis	12	10	*83*	21	13	*62*	33	23	*70*

In summary, the prognosis for the patients without carditis when treatment is started (Group A) is excellent. None had died and 92% were without apparent heart disease five years later.

CARDIAC GROUP B

Of the 252 patients in this category originally admitted to the study 5 had died, 10 were known to be alive, although their cardiac status was unknown, and the cardiac status at 5 years had been recorded for 221. The remaining 16 had been lost to follow-up (Table I). As has already been shown, the group is clinically heterogeneous and for analysis of the 5-year results has been subdivided (Table V) into five subgroups of murmurs (without failure and/or pericarditis) and one subgroup comprising patients with failure and/or pericarditis. The number of untraced cases was spread evenly over these subgroups. From the total figures (U.K. and U.S.A.) the following results may be noted:

1. *Patients with a grade I apical systolic murmur alone*

Of the 39 patients with only a grade I apical systolic murmur at the start of treatment, 14, or 36%, had murmurs at 1 year, while at 5 years the number had fallen to 7, or 18% (3 with a grade I apical systolic murmur, 1 with a grade II apical systolic murmur, 1 with apical systolic and mid-diastolic murmurs, 1 with basal diastolic, apical systolic and mid-diastolic murmurs and 1 with apical systolic and pre-systolic murmurs). Thus 82% of this group had no apparent heart disease at 5 years and none had died.

2. *Patients with a grade II or III apical systolic murmur alone*

Of the 60 patients in this category 32, or 53%, had at least one cardiac murmur at 1 year. This figure had decreased considerably at 5 years to 19, or 32% (6 with grade I apical systolic murmurs, 5 with grade II or III apical systolic murmurs, 5 with apical systolic and mid-diastolic murmurs, 1 with basal diastolic and apical systolic murmurs and 2 with known but unspecified murmurs). Thus among these patients 68% had no apparent heart disease at 5 years. Two additional patients originally in this group had died, both in the first year.

*The questionable apical systolic murmur (P murmur) was defined differently in the United States than in the United Kingdom. This difference affects the comparison of the results between the countries and the interpretation of the natural history of the disease. In the U.S.A., each principal investigator was permitted to classify a doubtful apical systolic murmur as a P murmur. In the U.K., however, the Working Party agreed that each investigator make a firm decision as to the presence or absence of an apical systolic murmur at the time of admission of the cases to the study. (A few cases, 7, were called doubtful in the U.K.) In the U.K. some patients with doubtful apical systolic murmurs were unquestionably labelled "no murmur"; others were labelled "apical systolic murmur" and included in Group B.

3. *Patients with an apical systolic murmur of any grade plus an apical mid-diastolic murmur*

Of the 44 patients in this category 28, or 64%, had at least one murmur at 1 year, while at 5 years the number was 23, or 52% (6 with an apical systolic murmur grade I, 6 with an apical systolic murmur grade II or III, 4 with an apical systolic and an apical mid-diastolic murmur, 2 with a basal diastolic murmur and an apical systolic murmur and 3 with a basal diastolic murmur, an apical systolic and a mid-diastolic murmur, and finally 2 with an apical pre-systolic murmur accompanied by an apical systolic murmur in the first and by an apical systolic and a basal diastolic murmur in the second). Thus among these patients only about half (48%) had no apparent heart disease at 5 years. In addition one had died during the fourth year, but not from rheumatic fever.

4. *Patients with a basal diastolic murmur alone*

There were only 11 patients in this category of whom 5, or 45%, had at least one murmur at 1 year, decreasing to 3, or 27%, at 5 years (2 with basal diastolic murmurs alone and 1 with unspecified murmurs). Thus 73% of this group had no apparent heart disease at 5 years. None had died.

5. *Patients with a basal diastolic murmur and an an apical systolic and/or a mid-diastolic murmur*

Of the 34 patients in this category at 5 years, 33 were reported at 1 year, and of these, 22, or 67%, had at least one murmur at that time. The figure decreased to 18 out of 34 cases, or 53%, at 5 years (4 with a grade II apical systolic murmur, 1 with apical systolic and mid-diastolic murmurs, 1 with an apical mid-diastolic murmur alone, 7 with a basal diastolic murmur alone and 5 with a basal diastolic murmur and another murmur, 4 of which were apical systolic and 1 a mid-diastolic murmur). Thus almost one-half of this group (47%) had no apparent heart disease at 5 years. In addition one patient had died during the fifth year.

6. *Patients with failure and/or pericarditis*

Turning finally to the patients in Group B with failure and/or pericarditis at the start of treatment, we find 33 of whom 24, or 73%, had at least one murmur at 1 year. At five years 23, or 70%, had a murmur (4 with a grade I apical systolic murmur, 8 with a grade II or grade III apical systolic murmur, 3 with apical systolic and mid-diastolic murmurs, 2 with a basal diastolic murmur alone and 6 with a basal diastolic murmur and other murmurs of which 3 were apical systolic, 2 were apical systolic and mid-diastolic and 1 was apical pre-systolic and mid-diastolic). In other words, only 30% of this group were without apparent heart disease at 5 years. In addition one patient had died during the fourth year.

Comparison of the U.K. and U.S.A. experiences (Table V) reveals no consistent pattern of advantage or disadvantage. The largest difference, which lies in the group with basal diastolic plus other murmurs, is almost entirely a function of a differing standard of interpretation, since the U.K. figure is derived from one centre only. Thirty of the total 31 U.K. patients with a basal diastolic murmur at start of treatment whose status was known at five years were reported from this centre. The basal diastolic murmurs in cases at this centre were soft and 25 of the 30 disappeared.

TABLE VI.—CARDIAC GROUP B (CARDITIS PRESENT; NO PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS FOLLOWED UP FOR FIVE YEARS AND NUMBERS EXPECTED* AND OBSERVED TO HAVE MURMURS AT FIVE YEARS, ACCORDING TO SEX, AGE, DURATION FROM ONSET, AND PRESENCE OR ABSENCE OF VARIOUS SIGNS OR SYMPTOMS—U.K. AND U.S.A.

Status at start of treatment	*Number of cases*	*Number with murmurs at 5 years*	
		Observed	*Expected**
Males	104	41	44
Females	117	52	49
Under 10 years of age	119	55	54
10-16 years of age	102	38	39
0-14 days from onset	102	38	39
15 + days from onset	119	55	54
P-R .18+	54	15	20
P-R <.18	167	78	73
With joint involvement	76	26	30
Without joint involvement	145	67	63
With nodules	38	20	17
Without nodules	183	73	76
With chorea	30	8	11
Without chorea	191	85	82

*Expected numbers take account of differences in the severity of cardiac involvement among the groups being compared. They were calculated in the following manner: The proportions of cases with murmurs at 5 years were taken separately for the U.S.A. and the U.K. for each of the six cardiac subgroups in Group B. These proportions were applied in the U.S.A. and U.K. separately to the actual number of patients in each cardiac subgroup of the categories listed above to see how many in the small subgroups would have had a murmur at five years if they had experienced the total rate of occurrence. The "expected" numbers in the subgroups were added to get the total number expected in each category for the U.S.A. and U.K. combined.

An analysis was made of other factors which might have prognostic effects. These included sex, age, duration from onset and presence or absence at start of treatment of polyarthritis, nodules, chorea and prolonged P-R interval. None of these individually appeared to affect the evolution of rheumatic heart disease as measured by the presence of murmurs at 5 years (Table VI). Cardiac enlargement as measured by a cardiothoracic ratio on the teleoroentgenogram of 0.60 or greater was present at start of therapy in 16 Group B cases. In 13 of these at least one murmur was present at 5 years. This serious prognosis is explained by the large number of such patients (11 of 16) who had cardiac failure and/or pericarditis at start of treatment, practically all of whom (10 of 11) had at least one murmur at 5 years.

Twenty-five patients in Group B whose cardiac status at start of treatment was, on the average,

TABLE VII.—CARDIAC GROUP B (CARDITIS PRESENT; NO PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS WITH AND WITHOUT RETREATED RECURRENCES, AND PROPORTION WITH ONE OR MORE MURMURS AT 5 YEARS—U.K. AND U.S.A.

Cardiac subgroup at start of treatment	*Without retreated recurrences*			*With retreated recurrences*		
	No. of cases	*With murmurs at 5 years*		*No. of cases*	*With murmurs at 5 years*	
		No.	*%*		*No.*	*%*
Group B—carditis present; no pre-existing heart disease						
(1) One murmur, any grade	102	26	*25*	8	3	*38*
(2) Two or more murmurs, any grade	69	32	*46*	9	9	*100*
(3) With failure and/or pericarditis	25	16	*64*	8*	7	*88*

*Excludes one case with retreated recurrence which was not traced at 5 years.

more severe than in the other patients of Group B were retreated for recurrence (Table VII). At 5 years these retreated patients had a larger proportion of murmurs than those without retreated recurrences. However, the relationship between cardiac status at start of therapy and at five years still held despite retreated attacks in the interim. Among Group A cases there were no murmurs at 5 years in 9 patients with retreated recurrences; of Group B patients with a single murmur at start of treatment 3 out of 8 had murmurs at five years as compared with 9 out of 9 in patients with two or more murmurs and 7 out of 8 with failure and/or pericarditis.

From a summary of the cases in which there was carditis but no pre-existing heart disease (Group B), it is clear that prognosis is directly dependent on the amount and severity of cardiac involvement at the start of treatment, the proportion with a murmur at 5 years varying from 18% in those with a grade I apical systolic murmur to 70% among those with pericarditis and/or failure. Excluding the group with basal diastolic murmurs for the reason given above and because of the relatively few cases in this category in the U.S.A., we find that this trend holds when the figures are examined individually for each country. In addition, the proportion of all Group B cases with murmurs is remarkably similar in the two countries.

CARDIAC GROUP C

There were 102 patients of known cardiac status at 5 years who had definite or questionable pre-existing heart disease at the start of their treatment (Table VIII). Of the 80 without failure and/or pericarditis at that time, 70% had heart disease at 5 years and of the 22 with failure and/or pericarditis, all had heart disease. It may also be recalled that in addition 4 and 6 deaths from rheumatic fever had taken place respectively in these two groups and 1 death from other causes in the group without failure or pericarditis.

In Table IX all of the cases in the study in which there was follow-up for 5 years are listed in order of increasing severity of heart disease at start of treatment. It is abundantly clear that the range from 96% with normal hearts to 0%, at 5 years, is much more striking than differences reported here or ascribed elsewhere to the effects of treatment. Thus in the prevention of rheumatic heart disease no evaluation of therapy of acute rheumatic

TABLE VIII.—CARDIAC GROUP C (DEFINITE OR QUESTIONABLE PRE-EXISTING HEART DISEASE). NUMBER OF PATIENTS FOLLOWED UP FOR 5 YEARS AND PROPORTION WITH ONE OR MORE MURMURS AT THAT TIME—U.K., U.S.A., AND U.K. AND U.S.A.

Cardiac subgroup at start of treatment	*U.K.*			*U.S.A.*			*U.K. and U.S.A.*		
	No. of cases	*With murmurs at 5 years*		*No. of cases*	*With murmurs at 5 years*		*No. of cases*	*With murmurs at 5 years*	
		No.	*%*		*No.*	*%*		*No.*	*%*
Without failure and/or pericarditis	45	36	*80*	35	20	*57*	80	56	*70*
With failure and/or pericarditis	16	16	*100*	6	6	*100*	22	22	*100*

TABLE IX.—PROGNOSIS IN RELATION TO CARDIAC STATUS AT START OF TREATMENT—U.K. AND U.S.A.

Cardiac status at start of treatment	*No. of cases observed for 5 years*	*% with no murmur at 5 years*	*No. of deaths in 5 years*
Group A			
No carditis	71	*96*	0
Questionable carditis	32	*84*	0
Group B			
Apical systolic murmur grade I, only	39	*82*	0
Apical systolic murmur grade II or III, only	60	*68*	2
Apical systolic *and* apical mid-diastolic murmurs	44	*48*	1†
Basal diastolic with or without other murmurs	45/15)*	*53(27)**	1
Failure and/or pericarditis	33	*30*	1
Group C			
Pre-existing heart disease without failure and/or pericarditis	80	*30*	5‡
Pre-existing heart disease with failure and/or pericarditis	22	*0*	6

*Excluding one U.K. centre.
†Death from acute nephritis and uræmia.
‡Includes 1 death from acute intestinal obstruction.

fever can be valid unless this major factor is taken into account in the design of the study or the analysis of the data. This conclusion is reinforced by the facts that most of the deaths from rheumatic fever (10 of 14) were of patients with pre-existing heart disease, and that there were no deaths among those without heart involvement at start of treatment.

No comparisons have been made with the conflicting reports of results obtained with large-dose hormone therapy,[7-11] the most recent of which shows no advantage in a well-controlled study.[11] A firm decision on the efficacy of large-dose hormone treatment of rheumatic fever will depend on controlled studies of adequate size in which the status of the heart is similarly taken into account.

SUMMARY

A study has been made 5 years after the end of treatment of the 497 children who were admitted to the U.K.-U.S. co-operative clinical trial of the relative merits of ACTH, cortisone and aspirin in the treatment of acute rheumatic fever.

Of the 497 children, 445 (89.5%) were followed up for the complete 5 years, and the status of the heart was known for 426 of them. Only 16 (3.2%) had died, 14 of them from rheumatic heart disease; 36 (7.2%) were untraced. The very low fatality rate is striking.

At the end of 5 years, there is no evidence from the treatment schedule used in this study that the prognosis has been influenced more by one treatment than another. This confirms the findings reported at 1 year.

The major factor in determining the incidence of rheumatic heart disease at the end of 5 years is the status of the heart at the time treatment was begun. For patients without carditis initially, the prognosis was excellent, since in 96% there was no residual heart disease. In patients with carditis initially, but without pre-existing heart disease, the proportion without residual heart disease decreased progressively from 82% for those with only a grade I apical systolic murmur to 30% for those with failure and/or pericarditis. In patients with pre-existing heart disease, the prognosis was poor. Only 30% of those without pericarditis or failure and none of those with pericarditis and/or failure were without heart disease at 5 years.

Patients with carditis and without pre-existing heart disease who had recurrences which required retreatment during the follow-up period had on the average severer cardiac involvement at start of treatment than did those without recurrences requiring retreatment. At 5 years a larger proportion of these retreated patients had murmurs.

Treatment of acute rheumatic fever cannot be properly evaluated unless the status of the heart of the patients at the start of treatment is closely taken into account.

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MODERN TRENDS IN ACUTE RHEUMATIC FEVER*

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TWENTY YEARS ago rheumatic heart disease was the major cardiac problem in the pædiatric age group. This has changed over recent years for several good reasons: one is related to the slow but steady decline in the incidence of streptococcal disease, probably associated with the widespread use of antibiotics. Another is the improved social and economic conditions of the population, with less crowding in homes. A third is related to the changing times and our increased awareness of the large number of cases of congenital heart disease, it being fully realized for the first time that they are approximately ten times as common as heart disease of rheumatic origin in childhood.

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INCIDENCE

In 1941, the author summarized the incidence of rheumatic heart disease from numerous previous studies. At that time, it was generally considered that rheumatic heart disease occurred in approximately 2% of the school population. More recent reviews indicate that the incidence is now lower. Sampson (1945)[1] found it to be 0.38% in one group of school children and 2% in another group. Wedum (1945)[2] reported the incidence as 1.6%, Quinn (1946)[3] as 1%, Packard (1952)[4] as 0.32%, Quinn (1956)[5] as 2.2%, and Saslaw (1956)[6] as 0.3%.

In the cardiac registry for the city of Toronto (1948-1949) Gardiner and Keith[7] found an incidence of less than 0.3% (see Fig. 1). A diminishing incidence of rheumatic fever and rheumatic heart disease is reflected in the group shown in Fig. 2. A large number of patients were seen in the 1930's, but there has been a distinct falling off in the last 15 years. Hitchins (1958)[8] reports a similar drop in Cardiff, Wales, from the year 1931 to 1950.

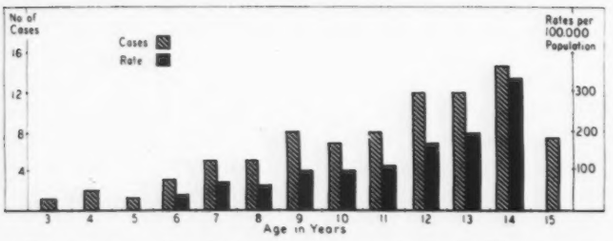

Fig. 1.—Age distribution of rheumatic heart disease recorded in the Toronto Heart Registry, 1948-1949. Rate of rheumatic heart disease per 100,000 population.

The discrepancy in the incidence figures quoted above is probably related to the difference in interpretation of mild or grade I murmurs in this group of school children. Some authors label such murmurs functional, when others would label them grade I organic.

It has now been shown conclusively that hæmolytic streptococcus Group A plays an intimate role in the etiology of rheumatic fever. In the studies

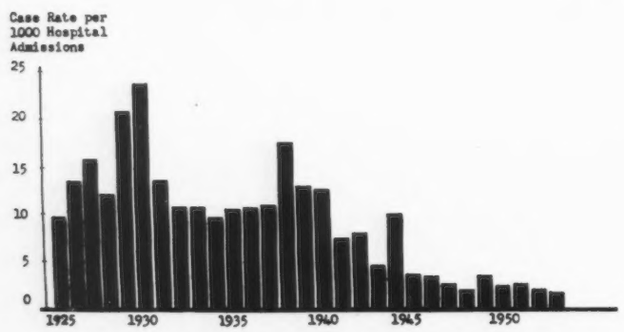

Fig. 2.—Incidence of rheumatic heart disease in relation to hospital admissions—The Hospital for Sick Children, Toronto, 1925-1953.

of service personnel during World War II, a relatively constant incidence of rheumatic fever was recognized after streptococcal epidemics in young adults (approximately 3%). The incidence of rheumatic fever after a Group A hæmolytic streptococcal infection in children has never been clearly delineated. It appears to be considerably lower than that among adults. The actual incidence of rheumatic heart disease in the school children of the city of Toronto would support this statement. Of 75,000 school children between the ages of six and 14, in the Toronto heart registry, Gardiner and Keith[7] found 120 cases of rheumatic heart disease. If each of the 75,000 school children had one streptococcal infection during their school years from six to 13 years of age, which would be a low estimate, and 3% developed acute rheumatic fever, one would expect 2250 cases of rheumatic fever. Since approximately half of these would have persistent heart disease, 1125 cases of rheumatic heart disease would be expected to turn up at examinations carried on through the heart registry. Actually, only one-tenth of this number has been recorded after careful study. Thus, the incidence of rheumatic heart disease after streptococcal infections is considerably lower than 3%, and probably in the neighbourhood of 0.3%, or one-tenth of those recorded in the adult investigations. This attack rate is supported by a recent study of Siegel *et al.*[28] who found that among 512 children with nasopharyngitis who had a Group A hæmolytic streptococcus by throat culture only 0.37% developed rheumatic fever as a sequela.

The relationship of the hæmolytic streptococcal Group A to rheumatic fever may be summarized as follows. First of all, there is a history of sore throat or upper respiratory infection in approximately two-thirds of cases. Epidemics of rheumatic fever are known to occur commonly after scarlet fever. The Group A hæmolytic streptococcus has been isolated in rheumatic fever in a high percentage of cases, much higher than that found in the ordinary population. Bacteriological studies have demonstrated significantly elevated streptococcal antibodies of one type or another in nearly 100% of cases of acute rheumatic fever. The attack rate of rheumatic fever after a hæmolytic streptococcal infection in young adults and service personnel has been relatively constant (3%). Finally, the prevention of rheumatic fever in a streptococcal epidemic may be achieved by treating all patients with streptococcal throat by adequate doses of penicillin.

In attempting to explain the difference in incidence of rheumatic fever after streptococcal infections in young adults as compared with children, Rammelkamp[9] suggests that an epidemic with a single virulent streptococcus Group A is more likely to produce active streptococcal disease and rheumatic fever than sporadic diversified hæmolytic streptococcal organisms intermittently active in a city population. This view is supported by the fact that a number of streptococcal epidemics in boys' boarding schools have a reported incidence of rheumatic fever that is close to the adult level. Siegel's findings lead to a similar conclusion.[28]

Since rheumatic fever is a complication of a streptococcal infection, it is of interest to notice what has happened to some of the other complications of streptococcal infections in the population of the Hospital for Sick Children over recent years.

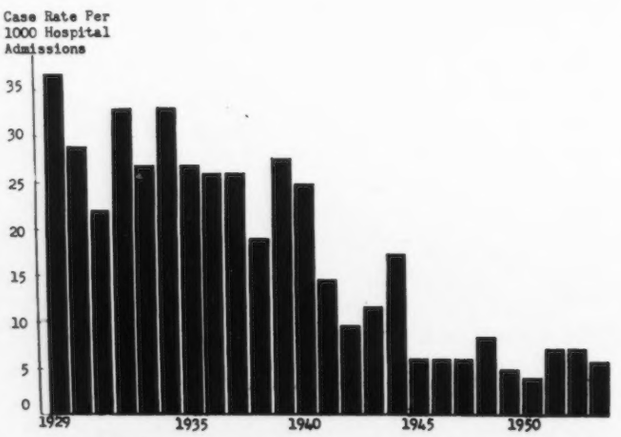

Fig. 3.—Incidence of mastoidectomy (frequently streptococcal in origin)—The Hospital for Sick Children, Toronto, 1929-1953.

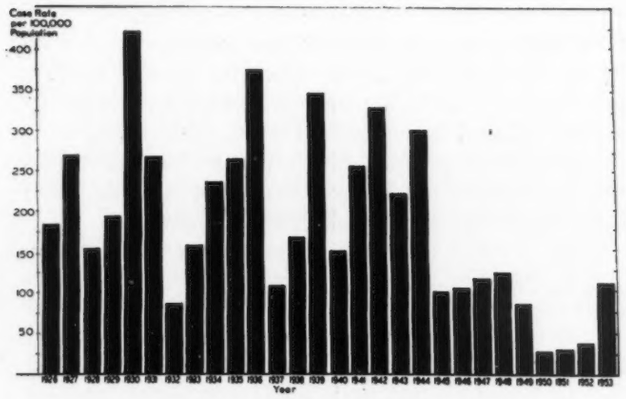

Fig. 4.—Incidence of scarlet fever—Department of Public Health, City of Toronto, 1926-1953.

Fig. 3 shows the incidence of mastoidectomies, and a distinct drop is seen after the years 1940-41. Fig. 4 gives the incidence of scarlet fever in the city of Toronto from 1926 to 1953, and again, there has been a drop in recent years. Fig. 5, showing the incidence of acute nephritis, reveals very little change over the years. Fig. 6, dealing with cervical adenitis, indicates a slight drop in recent years, but not the dramatic change shown in the other diseases.

DIAGNOSIS

The diagnosis of acute rheumatic fever has been made more uniform, and easier, by the Jones criteria.[10] Jones divided the diagnostic criteria into a major and a minor group, and required that two major criteria be present or one major and two minor for a clear-cut diagnosis of acute rheumatic fever. The major criteria were listed as rheumatic arthritis, carditis, nodules, chorea, and erythema marginatum. The minor criteria were set down as fever, raised sedimentation rate, lengthened conduction time, evidence of a preceding hæmolytic streptococcal infection, or a previous history of rheumatic fever.

These criteria tend to eliminate the doubtful cases. This has not proved a hardship, because the doubtful cases are usually not rheumatic in origin, and those that are, do not have and are unlikely to develop heart involvement. The chief

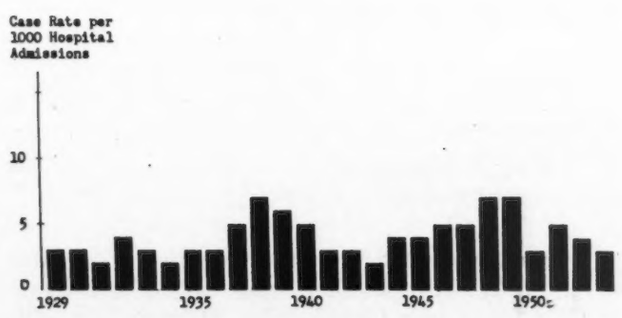

Fig. 5.—Incidence of acute nephritis and acute glomerulonephritis (usually streptococcal in origin) in relation to hospital admissions—The Hospital for Sick Children, Toronto, 1929-1953.

obligation that rests on the physician in making a diagnosis of possible rheumatic fever in a patient who does not satisfy the Jones criteria is to see that the child is observed until a diagnosis is made. In this way no harm will come to the patient during the acute stages of the disease. Recently, Saslaw[11] has favoured the use of a skin test in making the diagnosis of acute rheumatic fever in certain problem patients, especially those without evidence of heart involvement. This involves the use of Trafuril, which was developed by the Ciba Company as a rubefacient, but on trial was found to produce no redness in the skin in rheumatic fever and rheumatoid arthritis. In a normal child it causes an area of the skin to appear raised and red five or ten minutes after application. Absence of the normal red response in the skin, therefore, is suggestive evidence of rheumatic fever. This may be of some use in differentiating patients with upper respiratory infection and aches and pains from those with true rheumatic fever, and in such patients a red reaction in the skin is apparent. However, the response of the skin test

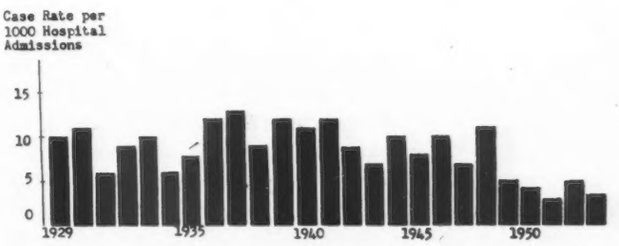

Fig. 6.—Incidence of cervical lymphadenitis (frequently streptococcal in origin)—The Hospital for Sick Children, Toronto, 1929-1953.

is not constant and is difficult to control. Its value is, therefore, limited.

Many conditions in the past have been suggested as diagnostic problems in relation to rheumatic fever, particularly those that cause aches or pains in the limbs. These include poliomyelitis, respiratory infections, subacute bacterial endocarditis, rheumatoid arthritis, growing pains, and the aches and pains that occur in a child in the evening after a day of strenuous physical activity.

None of these conditions cause much difficulty, but the last-mentioned is perhaps the most common. Since the heart is normal in such patients, the sedimentation rate is not elevated, and the pains are apt to be intermittent over a period of time without obvious infection, it is readily possible to recognize their benign nature.

The functional heart murmur may occasionally produce difficulties for the examining physician, but most functional murmurs are heard towards the midline from the apex or along the left sternal border, and are short and relatively insignificant, with coarse twanging-string characteristics. Tachycardia due to exercise, nervousness or infection may convert a slight functional murmur into one that is louder, and may suggest the presence of

Canad. M. A. J.
Oct. 8, 1960, vol. 83

mitral insufficiency. However, when the infection or excitement has subsided, this murmur assumes more benign proportions and can be recognized as such. The innocent murmur is never heard throughout all of systole and is usually maximal in mid-systole. It is best heard towards the midline from the apex or at the left sternal border, and is not propagated to the axilla.

TREATMENT

After the discovery by Maclagan (1876)[12] that salicylates were helpful in this condition, little change was made in therapy over many decades. However, in the past 20 years, several new methods of treatment have been introduced. These include antibiotics, salicylates of various types, and hormonal therapy. Although there is some difference of opinion in the use of these drugs, the chief controversy has concerned a comparison of the benefits of hormonal therapy and those of salicylates. In reviewing these data, there is not much to choose between them. Nodules and murmurs disappear more rapidly with hormonal therapy, and the conduction time of the electrocardiogram regains its normal value more rapidly. Murmurs also disappear more quickly over the first three months. At the end of one year there is no significant difference between the aspirin and the steroid group, as reported by the International Co-operative Study (1955):[13] a summary of these data is shown below. The persistence of residual cardiac damage is essentially the same in both groups. Since then Massell,[14] Illingworth,[15] Dorfman,[16] Kuttner,[17] and others, have used a wide variety of doses of hormones and salicylates to repeat this comparison. Massell,[14] Dorfman[16] and Gilbert[18] have presented findings that suggest that the hormones are superior to salicylates. Kuttner,[17] reporting a combined study, finds no difference between these two modes of therapy, and, if anything, her findings favour salicylates. Illingworth's[15] data indicate that the combined use of salicylates and cortisone is better than either used separately.

Hormone and Salicylate Therapy Compared

	Therapy	*Total cases*	*% with no murmurs 1-3 years' follow-up*
International Co-operative Study, 1955	ACTH	61	54
	Cortisone	75	60 (3 years)
	Aspirin	79	59
Illingworth, 1957	No special treatment or salicylates	84	54
	Cortisone	19	47 (1 year)
	Cortisone and salicylates	33	81
Dorfman, 1959	Aspirin and bed rest	67	62
	Cortisone (Comp. F) or Comp. F and aspirin	64	85 (1 year)
Kuttner *et al.*, 1959	Prednisone	30	40
	Aspirin	27	63 (1 year)

Each of these two methods can be used in a beneficial way. The steroids are perhaps more useful in the early stages in speeding up the healing process, and the salicylates are helpful in preventing or minimizing rebound when the hormone is stopped. They permit one to use the sedimentation rate as a guide to activity. This is not possible when the patient is receiving hormonal therapy.

Penicillin Therapy

It has been shown by Rammelkamp, Houser *et al.*[19] that if the hæmolytic streptococcal infection that precedes rheumatic fever is adequately treated by penicillin during the acute stages, rheumatic fever as a complication can be prevented. Later studies demonstrated that if a similar dosage of penicillin were given nine days after the beginning of a streptococcal infection, rheumatic fever could be prevented, but at this stage antibody is not prevented from appearing in the blood stream. More recently, Mortimer and Rammelkamp[20] have presented evidence that prolonged administration of high doses of penicillin in an acute attack of rheumatic fever will reduce the incidence of heart disease persisting at the end of one year in comparison with a group treated by salicylates alone without the help of penicillin. At the end of one year, in the cases that did not have "fixed" valvulitis to begin with, the incidence of heart disease among the untreated controls was two and one-half times that of those receiving penicillin.

Mortimer, Rammelkamp et al.—1959

Treatment	*No. of patients with no "fixed" heart disease*	*% with no heart disease at 1 year*
Penicillin and aspirin therapy	29	78

In a group of 57 patients with rheumatic fever treated at the Hospital for Sick Children in Toronto, 32 were found to have valvulitis at the start of therapy. These 57 children received either salicylates or a hormone, or a combination of salicylates and hormone. Each also received 600,000 units of benzathine penicillin on admission and once a week for two weeks. An evaluation of these at the end of one year showed the following changes:

The Hospital for Sick Children—1960

Treatment	*No. of cases (no previous heart disease)*	*% with no heart disease at 1 year*
Penicillin therapy plus hormone		
hormone+salicylates or salicylates alone	24	80

It is always difficult to compare one rheumatic fever study with another, and we do not know exactly what was included by Mortimer *et al.*[20] under the term "non-fixed" carditis, but we can report that in our series of patients without previ-

ous heart disease 80% had no evidence of valvulitis at the end of one year. This is a low incidence, lower than has usually been found in the past before the use of penicillin. There was no difference between these subgroups of therapy. We have had the impression that rheumatic fever has been milder in the past few years. Whether this is related to penicillin therapy is difficult to say.

While ours was not a controlled study, it does support the thesis put forward by Mortimer, Rammelkamp *et al.*[20] that inclusion of penicillin therapy is associated with a low incidence of cardiac involvement at the end of one year. The doses advocated by Mortimer, Rammelkamp *et al.*[20] are based on the thesis that the valvulitis may be caused by a bacterial infection in the heart valve itself, and that such high doses are needed to eradicate the organism under these circumstances. The doses used in our series are those that are thought to be suitable for the elimination of organisms from the nose and throat and, therefore, are of a much lower magnitude. This needs more clarification, but from the data available to date we would like to suggest that the doses of penicillin that clear the throat of streptococcus will produce the maximum beneficial effect that one would expect from penicillin therapy. This is supported by a finding that in children treated with these relatively modest doses, 80% were without murmurs at the end of one year, a finding that is similar to the results reported by Mortimer, Rammelkamp *et al.*[20] with larger doses.

Whether or not one accepts completely the findings of Mortimer, Rammelkamp *et al.*[20] regarding the dose of penicillin during the acute attack, there is no doubt about the strong case that can be made for administering penicillin during an attack of rheumatic fever. Certainly we know that the disease is produced by a streptococcal infection, and that if the streptococcal infection had been treated adequately by penicillin, rheumatic fever would not have occurred. Even if treatment is delayed after a streptococcal infection, rheumatic fever can often be prevented. Many patients with rheumatic fever are still harbouring the streptococci in virulent form, and the presence of these organisms may prolong the illness by causing continued infection. It would appear beyond question, therefore, that penicillin should be given during an attack of acute rheumatic fever, whatever stage is first presented to the physician.

Since 10-20% of school children are harbouring hæmolytic streptococcus in their throats, it is very easy for any patient to pick up the organism during convalescence or on returning to school. For this reason it is important to continue penicillin prophylaxis, preferably in the injectable form, until maximal improvement of heart and valves has taken place. We therefore recommend the use of benzathine penicillin 1,200,000 units once a month for the first year during and after an attack of acute rheumatic fever. If this mode of therapy causes some discomfort it is often difficult to have the patient accept it. Its importance during the convalescence of rheumatic fever can hardly be overemphasized, and if the parents can be persuaded to this point of view, the child will usually co-operate. At the end of the first year, close to the maximal improvement possible will be achieved, and one may reasonably turn to other forms of prophylaxis.

The preceding paragraphs have led us to consider what constitutes adequate penicillin therapy in treating the various stages of rheumatic fever.

Breese and Disney[21] studied the therapy of upper respiratory infections in a group of hæmolytic streptococcal infections in the child population, by using various forms of penicillin. The most satisfactory form appeared to be the long-acting benzathine penicillin given as 600,000 units by injection at the time of the acute disease. Eighty-four per cent of the children had their hæmolytic streptococci eliminated from the throat by this method. In the general population, therefore, when one suspects the presence of a hæmolytic streptococcal infection, a single injection of 600,000 units of benzathine penicillin would appear to be adequate for the non-rheumatic child. When one is dealing with a child who is known to have had rheumatic fever, one must rid the throat of streptococci with a greater degree of certainty, and it would appear reasonable to give 1,200,000 units of benzathine penicillin intramuscularly once a week for three doses during the acute disease, and then once a month for the succeeding year.

Combined Salicylate and Hormone Therapy

The experience of many physicians over many years has led to the conclusion that salicylates have a beneficial effect on the symptoms of rheumatic fever. The fever and the arthritis are controlled more rapidly than if no such therapy is given, and the patient looks and feels better. The same may be said for hormones, but, in addition, they make the nodules, heart murmurs, and the abnormal length of conduction time disappear more rapidly than is the case with salicylate therapy. Salicylates have a few advantages over hormonal therapy. During salicylate therapy the sedimentation rate gradually returns to normal over several weeks. The study of the other manifestations, as well as experience in handling these patients, has indicated that at this point the disease ceases to be active, and some of the restrictions can be lifted. In other words, the sedimentation rate is useful in deciding when the patient may be allowed up and when further activity may be permitted.

This is not the case with hormonal therapy, since it suppresses the sedimentation rate and makes it difficult to tell whether the disease has truly subsided. Furthermore, rebound phenomena are less likely to occur with salicylates and, if they do occur, are less severe after withdrawal of salicy-

lates than after withdrawal of hormones. Toxic reactions to salicylates, when they are given in doses of 1/2-2/3 grain/lb. body weight in 24 hours, are very infrequent and rarely cause trouble when they do occur. With hormonal therapy, and particularly prolonged hormonal therapy in large doses, one may encounter hypertension, convulsions, psychosis, fatty liver, ruptured duodenal ulcer, obesity, hirsutism and retention of body salt. These complications are less likely with the relatively short courses recommended below.

Thus, both salicylates and hormone therapy have features that favour their use in acute rheumatic fever. The hormones are particularly useful in the early stages and the salicylates in the later stages. Since their effects are not identical, it would seem reasonable to give them together from the beginning of the illness. In this way, 1/2-2/3 grain/lb. body weight, given every 24 hours and kept up for several weeks until after the sedimentation rate has become normal, is a helpful procedure. The work of Wilson[22] suggests that a short course of hormone therapy is just as effective as a prolonged one. One might, therefore, recommend that 50 or 60 mg. of prednisone be given daily for one week, with a gradual scaling down of the dose during the next week until it is eliminated entirely. Concomitant administration of salicylates will help to control any rebound phenomena when the hormone is stopped, and one may then have whatever beneficial effects may result from either form of therapy.

The following presents the details of the therapeutic regimen suggested above:

1. 1,200,000 units benzathine penicillin, intramuscularly, on admission and on the seventh and the fourteenth day, and once a month for one year thereafter.
2. Aspirin—1/2 grain/lb. daily for three months.
3. Prednisone dosage:

Days	*Prednisone*
1–7	60 mg. (15 mg. six-hourly)
8	50 " (12.5 mg. six-hourly)
9	40 " (10 mg. six-hourly)
10	30 " (7.5 mg. six-hourly)
11	20 " (5 mg. six-hourly)
12	15 " (5 mg. eight-hourly)
13	10 " (5 mg. twice daily)
14	5 " (2.5 mg. twice daily)

PROPHYLAXIS

Since Coburn[23] reported his studies on the prophylaxis of rheumatic fever 20 years ago, numerous clinical investigations have been carried out in an effort to demonstrate the superiority of one or other antibiotic preparation in this regard.

Both sulphonamides and penicillin have been widely used prophylactically. Perhaps one of the most authoritative reports of recent origin is that of Feinstein *et al.*,[24] who presented the results of a prophylactic study comparing benzathine penicillin intramuscularly with oral sulfadiazine and oral penicillin G (200,000 units daily). Benzathine penicillin intramuscularly is undoubtedly the best, giving a recurrence rate of 0.3%; oral penicillin in doses of 200,000 units daily, a rate of 5% recurrence, and sulfadiazine 1.9%. They concluded that the oral dose of penicillin is not adequate, and recommended a higher one, the exact amount to be decided upon after further investigation. The great advantage of the injectable benzathine penicillin appears to be due to two things: firstly, since the drug has been administered by the doctor intramuscularly, he knows that the patient has received it, whereas only two-thirds or three-quarters of the patients take the oral tablets with suitable regularity. Secondly, it eliminates the hæmolytic streptococci from the throat. Thus, it acts not only as a prophylactic measure, but as a therapeutic measure as well.

The only disadvantage of benzathine penicillin is that it must be given intramuscularly and usually leaves a residual pain at the site for several hours. If this discomfort could be elminated, it would be much more acceptable to the children concerned, though there would still be the handicap of having to administer it by needle injection. At present, in most centres, children are treated by oral prophylaxis using either sulfadiazine or penicillin. Kaplan[25] has demonstrated the value of phenoxyl methyl penicillin (penicillin V) by giving a dose of 200,000 units daily, and at the same time administering 1,000,000 units a day for ten days of the same preparation in the event of the hæmolytic streptococcal sore throat infection. This procedure kept the recurrence rate down to 2% for the first year and 0.4% for the second year. Phenoxyl methyl penicillin preparation appears to give a better blood level than penicillin G, and a considerably higher but shorter-lived curve than benzathine penicillin. Newer types of synthetic penicillin may give higher blood levels than either penicillin G or V, but even with higher levels for short periods, it is questionable whether this would be as effective as the constant therapeutic or prophylactic level achieved by a large single dose of benzathine penicillin once a month. One may conclude, therefore, that the best method of prophylaxis against hæmolytic streptococcal infection in a rheumatic patient is benzathine penicillin 1,200,000 units given once a month by injection. With this dose, the oral preparation to rival its effectiveness should achieve close to the same or somewhat similar blood levels. This would necessitate at least one tablet twice a day of oral penicillin, or a very large dose of benzathine penicillin by mouth once a day. At the present time, the expense of this form of prophylaxis is inordinately high.

One daily dose of sulphonamide is a reasonably satisfactory method of prophylaxis when given in the dose of 0.5 grain for children under 60 lb., and 1 grain for those over 60 lb. It will help to keep the throat clear of hæmolytic streptococcal infections, but will not clear the throat of hæmolytic streptococci as penicillin does. Its administration during an upper respiratory infection due to hæmolytic streptococci will not prevent rheumatic fever as a sequel.

Another alternative is the use of a daily dose of penicillin (400,000 units daily) and the administration of therapeutic doses of the semi-synthetic penicillin (Brocsil or Syncillin) in 400,000 units three or four times a day for six days in the event of any upper respiratory infection. It is necessary to treat most respiratory infections in this manner, since it is difficult to be certain whether one is dealing with a hæmolytic streptococcal infection or not, and the use of throat swabs or antistreptolysin titres delays therapy unnecessarily.

TABLE I.

	Incidence of carditis when last seen
Group A on receiving prophylaxis (well taken).....	45%
Group B, no or inadequate prophylaxis.....	59%

Effect of prophylaxis in children who have had previous rheumatic fever or rheumatic heart disease, followed-up in Cardiac Clinic, The Hospital for Sick Children, Toronto, for an average of three and a half years.

Our results with sulfadiazine prophylaxis are shown in Tables I and II. Half of the recurrences were among the small group who did not take the prophylaxis. Furthermore, it will be seen in Table II that the incidence of heart disease in the follow-up group was distinctly higher in those not taking the preventive measures.

TABLE II.

166 cases—Prophylaxis well taken—recurrence rate...	6%
34 cases—Prophylaxis poorly taken (off 1-5 years)—recurrence rate.....	35%

Incidence of heart disease in patients receiving adequate prophylaxis compared with those taking it at infrequent intervals, or not at all.

PROGNOSIS

There is evidence that the prognosis in rheumatic fever is improving each decade: mortality is falling, recurrences are less common, initial attacks appear to be less severe, streptococcal disease is more readily treated, and surgery for valvular stenosis or incompetence is becoming progressively better.

It has long been recognized that certain manifestations of rheumatic fever are less severe and more likely to be associated with a good prognosis than others: chorea is an example of this, since it carries a lower incidence of heart disease. But now it seems possible to make a reasonably accurate estimate of the prognosis in any one case on the basis of the findings during the first attack. Those with little or no cardiac involvement initially do well over the years, while those who react unfavourably in the initial stages do poorly in the long run.

The majority of children come out of an attack of acute rheumatic fever with little or no heart damage. Approximately 25% do not have any carditis, as indicated by heart murmurs during their first attack. In many the heart murmurs disappear in the next year or so, and in a few others new murmurs appear, so that at the end of five years of prophylaxis approximately 60% are without clinical evidence of valvulitis. Thus, if after the initial attack, recurrences can be prevented, there is no reason why a larger proportion of patients could not have their murmurs disappear, and why rheumatic fever could not be eventually reduced to an innocuous disease.

The data collected by the Co-operative Study[13] have been most helpful in permitting one to estimate more accurately the prognosis in the early stages of the disease. Thus in the five years of the follow-up the mortality was only 3.2%. This was lower than that reported by Schlesinger[26], 10%. Death from this condition in childhood is almost invariably associated with recurrent attacks, and usually for some time before the first stage one may recognize the enlarged heart and severe valvular involvement.

One of the most striking features for many years has been the recognition of a good prognosis in those who have rheumatic fever without evidence of heart disease in the early stages of their first attack (Keith[27]). In the Co-operative Study,[13] 88% of these children had no murmurs at one year, and 92% had no murmur at the end of five years.

Those with clinical evidence of carditis on admission to hospital can be subdivided according to the degree of the murmurs. Of those with grade I apical systolic murmurs alone, 64% had no murmurs at one year, but by five years nearly 82% had no murmurs and none had died.

Of those with grade II or grade III apical systolic murmurs, 47% had no murmurs at the end of one year. However, at the end of five years this had increased to 68% without murmurs. Two died in the five-year period, both in the first year.[13]

When an apical systolic murmur is accompanied by an apical mid-diastolic murmur, the prognosis is not quite as good as when the diastolic murmur is not present. Thirty-six per cent had no murmurs at the end of one year in this group, and at the end of five years 48% had no murmurs.

The most seriously involved group were those with congestive heart failure and/or pericarditis. Only 27% were free of murmurs at the end of one year, and this was much the same at the end of five years, the figure at that time being 30% without murmurs.

The aortic diastolic murmur will usually persist if it appears in rheumatic fever, but occasionally the new appearance of such a murmur should be recognized within the next few weeks. If it is present three or four months after onset, it will usually continue to be present for the life of the patient.

Pre-systolic murmurs also persist; changes are due to mechanics rather than a significant diminution of the organic valve disease. Such murmurs can, of course, be relieved by surgery. The mid-

Canad. M. A. J.
Oct. 8, 1960, vol. 83

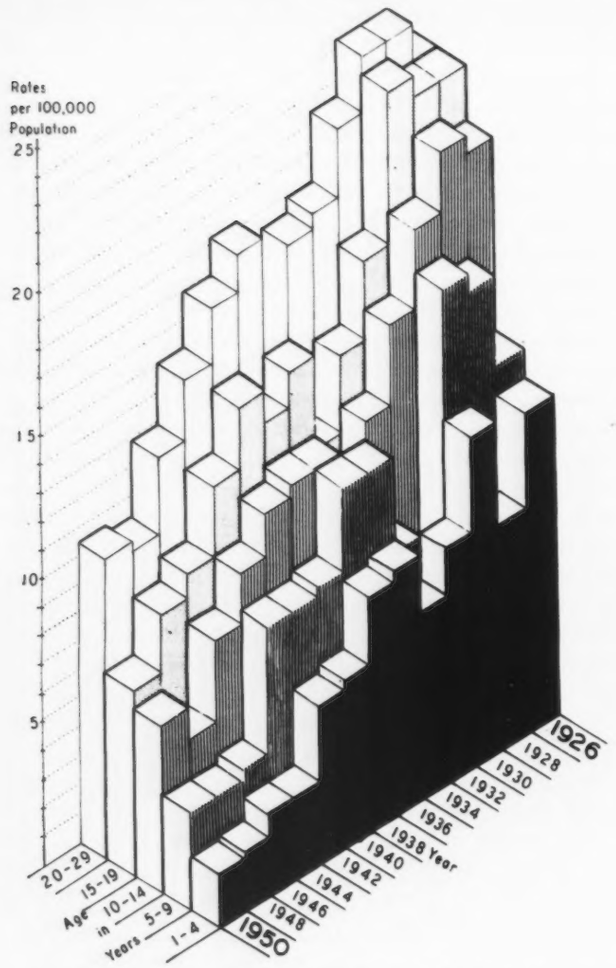

Fig. 7.—Deaths from heart disease in children and young adults, 1926-1950, Canadian Vital Statistics. (Courtesy The Macmillan Company, New York; from *Heart Disease in Infancy and Childhood*, by Keith, Rowe and Vlad.)

diastolic murmur of acute rheumatic fever in childhood has a different origin and is invariably associated with mitral insufficiency and a rapid inflow at the beginning of diastole. This murmur usually disappears as the patient improves and always ceases when the mitral systolic murmur disappears.

The prognosis of rheumatic fever and rheumatic heart disease is intimately related to the streptococcus, its prevalence and virulence in a community.

It may be difficult to recognize clinically a streptococcal infection in a child, since the vast majority of upper respiratory infections of other origins have similar signs, and they are far more common. It may not be possible to prevent initial attacks of rheumatic fever, but once the rheumatic subject is identified by the appearance of characteristic signs and symptoms, a great deal can be done in the treatment of the attack and prevention of recurrences. The outlook for these children, which once was so poor, is now greatly improved, as can be seen from the figures given above.

The falling mortality rate, as indicated in Fig. 7, should serve as a stimulus to all of us to treat these children to the best of our abilities, and further reduce the number of cases of myocarditis and valvular deformity. The means to do this, in the majority of cases, are now in our hands.

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THE CAUSE AND NATURE OF SCARLET FEVER

Sometimes the erroneous ideas of a great student of a disease—erroneous because he knew too much—set back the clock for many years. So it was with Georg Jochmann, the great student of infectious disease, and scarlet fever. At the time of Jochmann's paper, the relation of the streptococcus to scarlet fever seemed practically settled. But in a long and well-reasoned discussion, Jochmann finally concluded that the streptococcus was not the primary cause of scarlet fever but was simply responsible for the septic complications. On the strength of his prestige, this view was widely accepted, and the disease was put down as of unknown causation until the revival of interest in scarlet fever in the early twenties, especially by A. R. Dochez and by George and Gladys Dick.—A. L. Bloomfield: *A.M.A. Arch. Int. Med.*, 106: 293, 1960.

PATHOLOGY AND PATHOGENESIS OF THE DIFFUSE COLLAGEN DISEASES*

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PART III OF THREE PARTS

PATHOGENESIS OF THE COLLAGEN DISEASES

IN THIS last part an attempt will be made to give an account of recent morphological and experimental data pertinent to the pathogenesis of the collagen diseases. Firstly, the nature of fibrinoid and other changes in the intercellular connective tissue in these diseases will be discussed. Then, some new evidence—morphological, immunological and experimental—that the collagen diseases are diseases of hypersensitivity will be presented.

Fibrinoid

In all the collagen diseases fibrinoid occurs in the interstitial connective tissue, but most frequently in vessels. It is found not only in the collagen diseases but also in a variety of forms of damage to connective tissue.[58, 59] While fibrinoid may be abundant, some lesions contain none. Nevertheless, many investigators have attempted to identify the nature and origin of fibrinoid, in the hope of obtaining an insight into the pathogenesis of the diffuse collagen diseases.

The terms "fibrinoid substance" and "fibrinoid degeneration" were introduced in 1880 by Neumann.[103] In the long interval since then, the main point of controversy has been whether or not fibrinoid derives from an intrinsic alteration of the intercellular elements of connective tissue ("fibrinoid degeneration") or from extravasated plasma components, particularly fibrin ("fibrinoid deposition"). Those who think it is derived from tissue elements postulate its origin from collagen, ground substance or smooth muscle. On the other hand, those who believe that it is derived from the blood stream postulate its origin from fibrin and other serum proteins, or nucleoprotein (for a review of the subject see Movat[95]).

Between 1953 and 1956 we investigated lesions containing fibrinoid from the collagen and other diseases and from experimental lesions produced by injuring the connective tissue in a number of ways.[93, 94, 97, 99] Fibrinoid is defined as an intensely acidophilic, dense, refractile and homogeneous substance with staining characteristics similar to those of fibrin. Morphologically we observed in many lesions various transitions from delicate threads of fibrin forming a meshwork, to bands, clumps and large masses of fibrinoid showing the above characteristics (Figs. 15, 16, 19-21 in Part II). Histochemically the amino acids tyrosine, tryptophane, cysteine and cystine were demonstrable in fibrin and fibrinoid (Fig. 26). These amino acids are known to be absent or in very low concentration in connective tissue but are in high concentration in plasma proteins. Histoenzymatic studies were carried out using the enzymes collagenase, testicular hyaluronidase, trypsin and fibrinolysin (plasmin). When sections of tissue containing fibrinoid were incubated with collagenase or hyaluronidase, the collagen or ground substance would no longer be stained, while fibrinoid was unaltered. Trypsin and fibrinolysin digested fibrinoid and left the connective tissue unchanged (Figs. 27a-28b).

From these studies it was concluded that fibrinoid is not derived from degenerated connective tissue but from exuded plasma. In some lesions (e.g. fibrinoid of the Schwartzmann phenomenon, fibrinoid in placentæ) fibrin is the only constituent of fibrinoid. In the collagen diseases gamma globulin, or perhaps gamma globulin (antibody) and the antigen with which it had formed precipitates, may comprise a large portion of fibrinoid. This will be discussed more fully in connection with hypersensitivity and the collagen diseases. However, if fibrin, and perhaps also serum albumin,[34] are not present in the lesion, the above-described characteristics of fibrinoid, particularly the intense acidophilia, are not detectable.

Using a different technique, namely immunohistochemistry (fluorescent microscopy) for the identification of fibrinogen, Gitlin, Craig and Janeway[33] demonstrated that fibrinoid in the collagen diseases always contained fibrinogen. It may be stated here that this concept is not new, but dates back to Marchand,[73] who in 1896 pointed out that the fibrinoid described in 1880 by Neumann[103] is the result of an interstitial fibrinous inflammation. This was confirmed recently also by Meyer.[86]

Other changes in the intercellular elements of connective tissue may be mentioned briefly. They result from the same process, i.e. inflammation, which gives rise to fibrinoid. Mucinous œdema ("mucoid degeneration") is a swelling of the acid mucopolysaccharide-rich connective tissue, as it occurs particularly in the heart, vessels and joints. It results from an increased permeability of the tissues and exudation of protein-rich fluid. In tissues which are not rich in mucopolysaccharides such a process leads to interstitial serous inflammation.[117, 120] The protein-rich exudate, and also the fibrinoid if not too abundant, is organized and converted into fibrous connective tissue (sclerosis). However, if the material which is to be organized is too abundant or the organization inadequate, the protein material undergoes hyalinization. This

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Canad. M. A. J.
Oct. 8, 1960, vol. 83

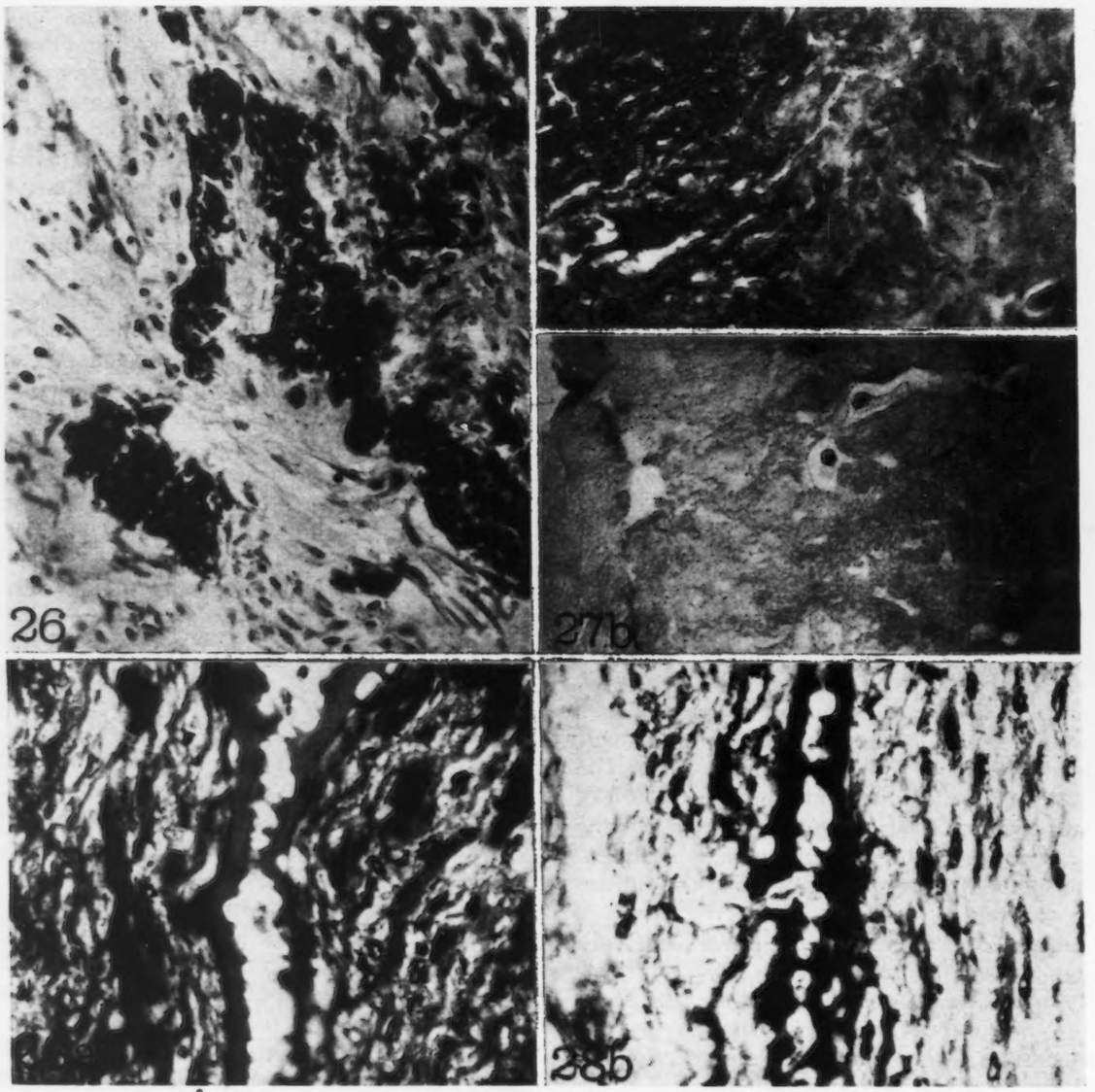


Fig. 26.—Fibrinoid in mitral valve in disseminated lupus erythematosus. The Barnett-Seligman reaction (after treatment with thioglycolic acid) shows the presence of cysteine and cystine in fibrinoid. The ground substance of the valve is not stained. × 320. **Fig. 27 (a) and (b).**—Control section (27a) and section treated with fibrinolysin (27b). In the control section the fibrinoid is seen in the left half of the photograph (black in photograph, intense red in section). In the treated section fibrinoid was no longer stainable. Masson's trichrome, × 425. **Fig. 28 (a) and (b).**—Control section (28a) and section treated with collagenase (28b). In the control section the fibrinoid was red and the collagen blue. In the section treated with collagenase the fibrinoid remained red (dark grey in photograph) and the collagen could no longer be stained. The cells were not affected by the collagenase. Masson's trichrome, × 425.

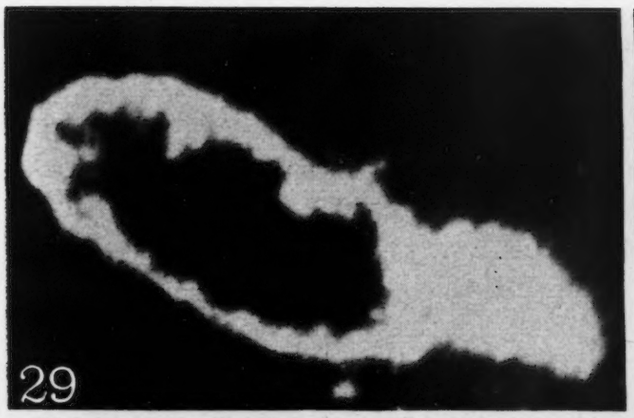
merely represents an alteration in the physical state of the extravasated protein, best described as ageing.

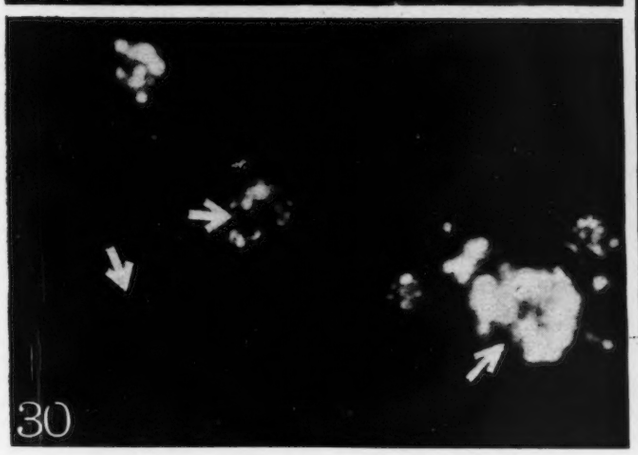
HYPERSENSITIVITY AND THE COLLAGEN DISEASES

a. *Morphological Evidence*

The concept of the "diffuse collagen diseases" was coined in 1942 by Klemperer, Pollak and Baehr.[57] However, a little more than a decade before, Klinge[60] had studied some of these diseases and had come to the conclusion, mainly from comparative experimental studies, that the "rheumatic diseases" develop on the basis of tissue hypersensitivity ("Hyperergy"). Tissue hypersensitivity or allergic-hyperergic inflammation has been studied in great detail by Rössle and his pupils.[114-116, 118, 119] While Klemperer[57-59] denied an allergic pathogenesis, at least in some of the collagen diseases, Rich[111] showed that there was circumstantial evidence of hypersensitivity in some cases and that the tissue changes were very similar to if not identical with lesions induced in rabbits by foreign protein. Ehrich[20] postulated that "the common denominator of the various collagen diseases lies in their pathogenesis, or more precisely, in the production by these diseases of abnormal gamma globulins apparently by plasma cells causing injury of the general mesenchyme".

In experiments dealing with local lesions produced by hypersensitivity (Arthus phenomenon) it was shown that the lesion consists of two components. One is an inflammatory reaction resulting from interaction of injected antigen and circulating antibody. The other, consisting of proliferation of plasma cells, represents the result of antigenic





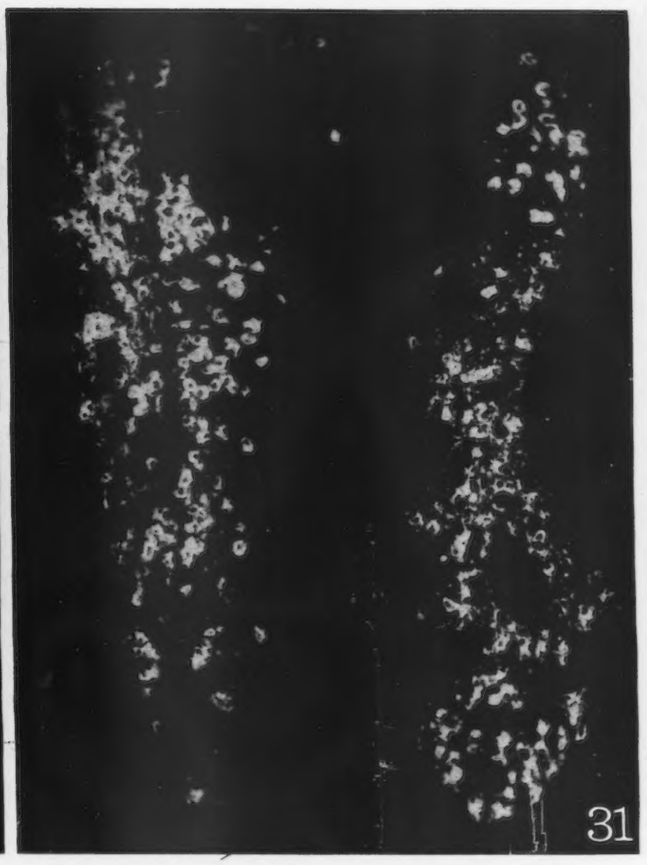


Fig 29.—Fluorescent micrograph of arterial lesion in the Arthus phenomenon. The fluorescent material (white in photograph, apple-green fluorescence in slide when examined in ultraviolet light) represents localization of antigen in the arterial wall. This is the site of interaction between the injected antigen and circulating antibody. × 350. **Fig. 30.**—This photograph shows the localization of antigen (or antigen-antibody complexes) in macrophages in the Arthus phenomenon. The site of the nucleus in the cells is indicated by arrows. The fluorescent antigen is present in the form of phagocytosed globules in the cytoplasm. × 1500. **Fig. 31.**—This photomicrograph shows numerous plasma cells of the synovial membrane from a patient with rheumatoid arthritis. The cytoplasm of the plasma cells contains the rheumatoid factor. Note the black area in the centre of many cells, representing the nucleus. × 150. (Courtesy of Dr. R. C. Mellors.)

stimulation of primitive mesenchymal cells and is the morphological counterpart of antibody formation.[89, 92] These experiments were extended to systemic sensitization and resulted in lesions throughout the connective tissue.[90, 96] Changes either not described before, or described but not considered to be of significance, were the proliferation of plasma cells both in the hæmopoietic tissues and in the lesions of connective tissue. When lesions of the diffuse collagen diseases were examined, they were also found to contain varying numbers of plasma cells.[90, 96] Here too the plasma cells had accumulated in both reticuloendothelial tissues and in the connective tissue; in the latter at the periphery of the acute inflammatory and necrotizing lesions. The conclusion from these studies was that the plasma cells in these lesions represent indirect morphological evidence of a local immune mechanism.

b. *Immuno-histochemical Evidence*

Studies using the fluorescent technique for demonstration of antigen and antibody in tissues (Figs. 29-31) likewise represent indirect evidence of a local hypersensitive mechanism. This immuno-histochemical evidence is based on the demonstration of gamma globulin in the various lesions of the collagen diseases. Antibody is produced in rabbits against human gamma globulin. The rabbit antibody is labelled with a dye which fluoresces in ultraviolet light. Frozen sections containing the lesion are covered with the labelled anti-human gamma globulin. After washing, the sections are examined in a fluorescent microscope (ultraviolet light source). Areas of fluorescence indicate sites of reaction between human gamma globulin (present in the lesions) and the labelled anti-human gamma globulin. Mellors and Ortega[79, 80] were the first to demonstrate gamma globulin in lesions of polyarteritis nodosa and acute disseminated lupus erythematosus. Vazquez and Dixon[133, 134] showed localization of gamma globulin in rheumatic fever, disseminated lupus and rheumatoid arthritis. Using basically the same fluorescent technique, Friou[28] and later Holborow *et al.*[49] demonstrated a serum factor in disseminated lupus erythematosus with an affinity for tissue nuclei. Recently Bardawil *et al.*[4] showed a similar serum factor in patients with lupus, scleroderma and dermatomyositis. This factor which resides in the gamma-globulin fraction and is thought to be an antibody is also responsible for the L.E. cell phenomenon. Mellors *et al.*[80] and Vazquez and Dixon[133] had already demonstrated gamma

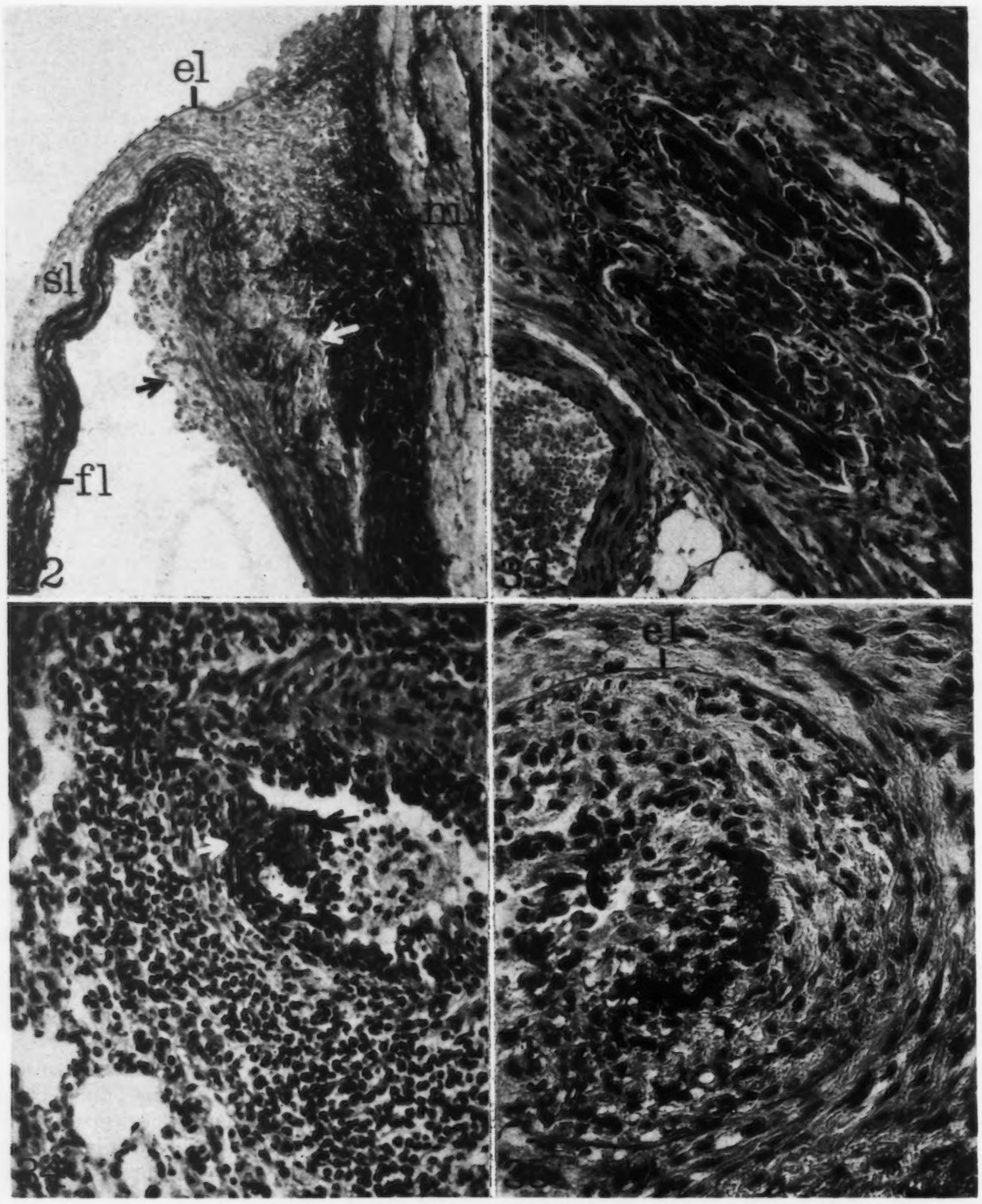


Fig. 32.—Mitral valve of rabbit with experimental serum sickness. There is some subendothelial cellular reaction to the right of the area marked "el" (elastic membrane). More cellular reaction and mucinous swelling of the connective tissue is seen between the two arrows at the base of the valve (Sl = spongiosa layer, blue in section; fl = fibrosa layer, dark red; m = myocardium, yellow). Pentachrome II, × 130. **Fig. 33.**—Circumscribed acute lesion in myocardium of rabbit injected with a single large dose of foreign protein. There is necrosis of muscle fibres and a mononuclear cell reaction. The large cells are myogenic giant cells (mg). Hæmalum, phloxine-saffron. × 255. **Fig. 34.**—Acute arteritis of pulmonary artery in serum sickness. The arrows indicate a protein deposit (presumably antigen-antibody complexes) adherent to the endothelium. The endothelial cells have increased in number and size. The media in the lower half of the artery is completely replaced by inflammatory cells. The inflammatory cells around the vessel could be identified in the microscope as macrophages and rabbit pseudo-eosinophils. Masson's erythrosine, orange G and toluidine blue, × 255. **Fig. 35.**—Subacute arteritis of coronary artery of rabbit which has received multiple intravenous injections of horse serum. There is intense proliferation of cells inside the internal elastic lamina (el). Almost all cells are mononuclears. Fibrinoid is deposited between the proliferating cells. The lumen has been reduced to a narrow slit. Phosphotungstic acid hæmatoxylin, × 330.

globulin in the L.E. cell. Quite recently Mellors *et al.*,[81] using the same technique, showed the localization (presumably formation) of the rheumatoid factor in plasma cells in synovial tissue (Fig. 31) and in lymph nodes and in germinal centre cells of lymph follicles in patients with rheumatoid arthritis.

c. *Immunological Evidence*

The fact that hypersensitivity is instrumental in the development of *rheumatic fever* has been accepted for some time. The etiological agent is the Group A hæmolytic streptococcus. The development of rheumatic fever is usually preceded 2-3 weeks by a Group A streptococcal infection,

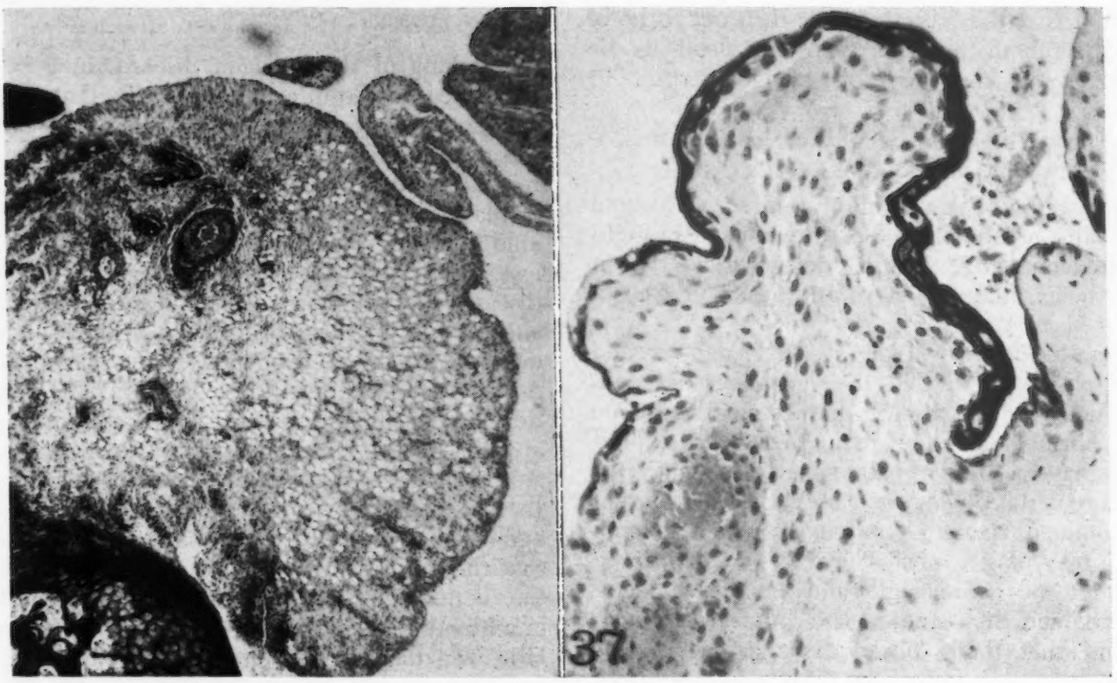


Fig. 36.—Acute allergic arthritis of rabbit. The photograph shows swelling of a synovial villus and accumulation of cells in the connective tissue, mainly around vessels. At high magnification many of the cells could be identified as immature and mature plasma cells. Pentachrome II, × 60. Fig. 37.—Chronic allergic arthritis of rabbit. A band of fibrinoid covers the synovial tissue. The loose connective tissue beneath the fibrinoid contains many fibroblasts and histiocytes. Phosphotungstic acid hæmatoxylin, × 210.

although in some cases the infection may be mild and remain undetected. The streptococcus produces a protein (streptolysin O), and antibody against this antigen (antistreptolysin O) is elevated in most cases of acute rheumatic fever. Recently[131] antibodies have been demonstrated also against other streptococcal antigens (antistreptodornase B). This was found elevated in many cases in which antistreptolysin O titre was low or borderline.

The nature of antinuclear antibodies in *systemic lupus erythematosus* was extensively investigated in recent years. Klemperer thought that the alteration in the L.E. cell phenomenon is a depolymerization of the desoxyribonucleic acid (DNA) of the nucleus. Later it was shown that there was no depolymerization, but a rise in nuclear protein, owing presumably to a combination of the L.E. cell factor (a gamma globulin) with DNA. The demonstration that the L.E. cell factor is an antibody was stepwise. First it was shown[87] that the L.E. cell factor can be removed from the serum by isolated cell nuclei. Then it was shown that instead of whole nuclei, isolated desoxyribonucleoprotein (DNA plus histone) could be used.[50] Recently Holman[51] demonstrated that the L.E. cell factor, which has been isolated in purified form, possesses the physical and immunological characteristics of antibody globulin. He postulated that the reaction in the L.E. cell phenomenon is an immunological one, in which the nucleoprotein is the antigen, and the L.E. cell factor the antibody. Other serum factors have been found in disseminated lupus erythematosus, by using complement fixation and precipitin reactions.[15, 113] These factors also have the characteristics of antibody gamma globulin.

The exact role of antinuclear antibodies in acute disseminated lupus has not been established. Holman[51] suggests that they are merely by-products of a severely altered immunological mechanism and that they have no primary pathogenetic significance.

Sera of patients suffering from *rheumatoid arthritis* contain a gamma-globulin fraction referred to as rheumatoid, RA or Waaler-Rose factor.[132, 144] It is used as "antibody" in the various serological tests for rheumatoid arthritis. The "antigen" used in the original test was sheep red cells sensitized by other red cells, e.g. human, guinea pig, alligator. Cells have also been coated with human gamma globulin (after treatment of the cells with tannic acid in order to enhance non-specific binding of gamma globulin). The essential feature in the reaction is that the RA factor reacts in all these tests, not with the cells, but with the coating material (gamma globulin). It is possible to use, instead of coated cells, latex particles, made antigenic by coating with human gamma globulin. The most convincing evidence that the RA factor reacts with gamma globulin was presented by Epstein *et al.*,[22] who demonstrated a precipitin reaction using gamma globulin and RA factor. The gamma globulin, acting as an "antigen" in both the agglutination and precipitin reactions, has been referred to as "reactant".[23] Ultracentrifuge studies indicate that the "reactant" resides in the 7 S fraction, whereas the RA factor resides in the 19 S fraction of gamma globulin.[26, 27] The "reactant" is species non-specific. Most investigators agree that the rheumatoid factor is most likely an antibody, perhaps an auto-antibody. Whether it has any role in the production of the disease remains to be established. It has been

suggested that the "reaction may turn out to be of the Wassermann reaction type and lead us no further towards knowledge of pathogenesis . . . "[110]

d. *Experimental Serum Sickness and the Collagen Diseases*

The injection of one or multiple doses of foreign protein into a rabbit gives rise to lesions throughout the connective tissue, but particularly in vessels, heart, lungs, kidneys and joints (Figs. 32-37).[60, 90, 96, 111, 146]

In connection with their studies Vazquez and Dixon[133] have stated that their "findings are consistent with the possibility that connective tissue edema, fibrinoid and fibrosis in the above studied diseases have a similar pathogenesis, or that they are different morphological states in the evolution of a common tissue alteration in which gamma globulin may play a role." They concluded that the localization of gamma globulin in the collagen diseases which they studied is a "preferential process" and that their "observations are consistent with, but not specific for, the presence of antigen-antibody reaction in the tissue lesions". The question still remains open as to how and where such an antigen-antibody reaction takes place. One is tempted to speculate that lesions in humans develop in a similar manner to lesions in animals. Recently Germuth[29, 30] and Dixon *et al.*[16] have put forward the hypothesis, based on some experimental evidence, that lesions of systemic hypersensitivity in animals (serum sickness) develop from interaction of antigen and antibody in the circulation and formation of soluble complexes which are pathogenic. Intravenous injection of such soluble antigen-antibody complexes formed *in vitro* into normal, unsensitized guinea pigs caused anaphylactic shock.[30] Injection of complexes into the skin of normal animals causes an acute, transient, inflammatory reaction.[14] Studies in our laboratory show that such complexes, when soluble, cause a transient inflammation, but when precipitated, cause a severe inflammatory lesion which heals by sclerosis.[128] Whether such antigen-antibody complexes formed in the circulation and precipitated in the tissues initiate the acute lesions in the collagen diseases remains to be investigated. If one accepts the hypothesis that antigen-antibody interaction is responsible for the development of the inflammatory lesions in the collagen diseases, one can go one step further in speculating that the early acute lesion is initiated by interaction of antigen and antibody with antigen in excess (soluble complexes). As the antibody titre rises, a stage is reached at which antigen and antibody are at equivalence and form precipitated complexes. These complexes are deposited at the sites injured by the soluble complexes. These precipitates and the exuded plasma proteins then form the matrix from which a dense and often hyaline sclerotic tissue develops. The latter represents the end stage of the lesion in the connective tissue.

CONCLUSIONS

Speaking of the collagen diseases in general, it seems reasonable to conclude, *firstly*, that fibrinoid, the characteristic change in these diseases, is not an intrinsic alteration of connective tissue, but the result of exudation, precipitation and inspissation of plasma proteins; *secondly*, that there is considerable evidence – morphological, immunological and experimental–that the lesions of the diffuse collagen diseases are somehow related to an immune mechanism. Only in rheumatic fever is there conclusive evidence that an exogenous agent, namely the β-hæmolytic streptococcus, is implicated in the development of the disease. In some cases of polyarteritis nodosa exogenous agents such as sulphonamide, iodine or penicillin, have been identified. In the other conditions of the group no exogenous agent is known and the currently accepted view is that they represent an altered state of reactivity of the tissues, which involves perhaps the production of antibodies against endogenous tissue components. However, the exact mechanism by which the various lesions are induced still awaits investigation.

"It seems clear that the answer to the problem can come only from combined research in the fields of clinical science–the planned study of diseases and its phenomenon in people who are ill; and basic science–the study of the structure and function of the fundamental connective tissues themselves."[18]

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IMIPRAMINE (TOFRANIL) IN MENTAL HEALTH CLINIC AND PRIVATE PRACTICE*

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THE OBJECT of this paper is to describe the effect of imipramine (Tofranil) in 59 patients. We have regarded the drug as already of proven effectiveness in the treatment of depression, but are concerned with its effectiveness and side effects in early ambulant depressives. Other studies have so far been chiefly concerned with more severely ill hospital patients whose depressions have been of longer duration.

RESULTS

Thirty-four patients began to improve after four or five days and were free of symptoms within two to three weeks. Thirteen had a delayed response, only beginning to improve after a week or longer. One began responding after five weeks and was well within six weeks, but here the possibility of spontaneous remission cannot be excluded.

Table I summarizes our results.

Complete or nearly complete recovery occurred in 40 out of 59 (67.8%). Twenty-seven out of 33 (80.2%) endogenous depressives recovered. The remaining cases (reactive depressions and patients in whom depression formed part of another syndrome) had a recovery rate of 50% (13 out of 26).

TABLE I

	Endogenous depression	*Reactive depression*	*Psychoneurotic depression*	*Schizo-affective*	*Total*
Recovered or greatly improved	27	5	8	0	40 (67.8%)
Slight to moderate improvement	2	2	4	0	8 (13.5%)
No improvement	4	1	4	2	11 (18.6%)
TOTAL	33	8	16	2	59

A standard dosage was used, 25 mg. thrice daily for the first week, followed by 50 mg. thrice daily until symptom-free, after which it was reduced to a maintenance dosage of 25 mg. thrice daily for six weeks. The drug was then discontinued. Patients selected were those with depression, indecision, loss of interest, retardation, somatic symptoms, exhaustion, loss of weight, etc.; the more advanced ones had ideas of hopelessness, self-blame and suicidal feelings. In only six of the group had the illness progressed as far as to include these latter symptoms. Fifty-two had been ill between one and six months, while seven had been ill for longer. Psychotherapy was given concurrently to the extent to which it was indicated.

A number of papers from both Europe and North America have recorded favourable results with the use of imipramine, for example Pollack,[11] Kuhn,[7] and Fazio, Giberti and Loeb.[5] Controlled studies have also been carried out by Lehmann, Cahn and de Verteuil[8] and by Ball and Kiloh.[2] Straker,[14] in reviewing the results from use of imipramine in private practice, also deals with case material similar to our own. It was interesting to note, however, that our patients were much younger than his (25% above the age of 50 as compared with 58% in Straker's series). We have observed that depression seems to strike a younger population in Cape Breton Island than elsewhere; in the authors' previous experience in England, for example, the percentage of depressives over 50 would have been even greater than Straker's.

Three cases showed drug resistance after an initially good response. One patient, a doctor's wife, aged 35, with a history of recurrent depression since the age of 19, was symptom-free after receiving the drug for ten days. She continued with a dosage of 50 mg. thrice daily, but after being well for six weeks relapsed. However, she became symptom-free after one electroconvulsive treatment (E.C.T.) and has for the past four months remained well on a maintenance dosage of 25 mg. thrice daily. Another patient relapsed after being well for four weeks on a maintenance dosage of 25 mg. thrice daily, but responded to a further two weeks of 50 mg. thrice daily, after which it was possible again to reduce the dosage. A third patient became resistant to the drug after three symptom-free weeks, and increased dosage was ineffective. We had several instances of apparent drug resistance in which investigation showed that the drug was not being taken, but there was little doubt that these three patients had been taking the drug. Two other patients had a relapse but became well on being returned to a maintenance dosage. However, since this trial began only nine months ago, further relapses are possible.

No patient has been recorded as improved unless there was some relief of the depression. It is interesting to note that only one out of 59 failed to improve in appetite and sleep, even when other symptoms remained unchanged.

SIDE EFFECTS

Side effects included dry mouth (three), sweats (three), giddiness (four), increased anxiety and agitation (one), insomnia (two), rash (two),

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hypotension (one), hypomania or mania (three), and acute confusional state (one).

One patient, a married woman of 38, developed a peculiar syndrome of bilateral proptosis, lid lag, and a pulse of 116. This came on after six weeks of treatment with the drug, the patient by then being free of depression. Thyrotoxicosis was suspected but tests failed to confirm this. A week later the patient gave up taking imipramine. After a further two weeks she was seen again when the depression had returned, accompanied by a number of delusions; for example, the thought would come into her head, "If you wash the crockery, you will kill the baby." Before treatment with imipramine she had never experienced obsessional symptoms. Imipramine was restarted at a dosage of 50 mg. thrice daily. After a week the depression was much less and obsessional thoughts were less obtrusive. Five weeks later she was free of symptoms. There was no return of the signs simulating thyrotoxicosis.

A 58-year-old woman with a history of previous depressive breakdowns, for which she had been admitted to mental hospitals, responded well to imipramine therapy and was symptom-free after 14 days. Dosage was reduced to 25 mg. thrice daily. Eleven days later she suddenly became confused and excited. The clinical picture was so flamboyant that it reminded one of a hysterical pseudopsychosis. She was admitted to a mental hospital and given no medication. After three days she was clearly orientated but in a state of hypomania. After a further four days she was normal and was sent home after a total stay in hospital of 10 days. She had had no previous manic attacks.

Another patient, a married woman of 31, without any previous attack of mania, developed a hypomanic syndrome after becoming free of symptoms and having taken 25 mg. thrice daily. She was admitted to a mental hospital in another city, from which she was sent home well after a period of six weeks. A month later she noted a return of depressive symptoms and began taking imipramine again without medical advice. However, there was no return of her manic symptoms. A third patient developed a hypomanic state which continued. He had had previous similar episodes so that this may have been fortuitous. Also, a married woman of 35, without previous psychotic episodes, developed an acute confusional state while receiving 25 mg. of imipramine thrice daily. She was admitted to a general hospital and responded to 100 mg. of chlorpromazine eight-hourly for 48 hours. One man of 67 with Paget's disease and a history of congestive heart failure developed hypotensive symptoms, but we had no serious trouble in this regard.

Routine laboratory tests were not carried out, but white cell counts were done immediately upon a complaint of sore throat or other suspicious symptoms. Two patients developed blotchy dark red macules over face and limbs that caused them to give up the drug.

DISCUSSION

In our series 68% recovered or were greatly improved. This resembles closely the findings of other authors, e.g. Kielholz and Battegay,[6] 67%; Lehmann *et al.*,[8] 60%; Straker,[14] 80%; and Mann and MacPherson,[10] 63% recovered or much improved. Azima and Vispo[1] found that 53.6% were markedly improved and that 40% were moderately improved. Pollack[11] found that 56% were much improved but when these categories were broken down, 70% of manic depressives (equivalent to endogenous depressives in our series) and 72% of reactive depressives were improved.

We found that 82% of our patients with endogenous depression recovered or were greatly improved. The figure for reactive depression was 50% and for psychoneurotic depression 63%. The consensus of other authors is that patients with endogenous depression do best, but that the depression of other syndromes often shows a favourable response. In the case of psychoneurotic depressions the drug seemed much more satisfactory than E.C.T., since it did not produce increased anxiety or depersonalization as electroplexy is liable to do in these patients. Also, there was no fear of treatment, and concurrent psychotherapy was not interfered with, except of course that one had to keep in mind the possible symbolic effect of giving a drug to a patient.

Patients with endogenous depression who did not improve or were only moderately improved showed no particular distinguishing features. One failed to respond to E.C.T., while two others responded slowly. Two who had refused further treatment because of a rash, responded to phenelzine. For patients with reactive depressions and psychoneurotic depressions, good results depended largely on the adequacy of previous personality. The complaint of definite loss of interest in life correlated well with a good result. There were two cases of obsessive-compulsive neurosis complicated by depression. Both were of long standing; one patient failed to respond at all, and the other did remarkably well after having shown no improvement with psychotherapy and several courses of E.C.T. This good response of obsessional symptoms suggests that the drug would be worth trying in cases of pure obsessive-compulsive neurosis. We have not had a single patient with this condition uncomplicated by depression in 800 cases seen at this clinic.

Many authors report little trouble from side effects in large series of cases—for example, Pollack[11] with 273 cases, Azima and Vispo[1] with 145 cases, and Kuhn[7] with 500 cases. Kielholz and Battegay[6] describe a case of circulatory collapse, and Lehmann *et al.*[8] one of myocardial infarction which may possibly have been associated with the drug. Sloman[13] describes a case of myocardial infarction during imipramine therapy and quotes five cases of cardiovascular complication from the literature. In his case he concludes that the infarc-

tion could be related to factors other than imipramine, and with the exception of one patient who took 100 25-mg. tablets in the course of one hour, this conclusion seems likely with regard to the other cases. At the June 1959 meeting of the Canadian Psychiatric Association five cardiac deaths, possibly associated with imipramine, were described. They tended to be of persons over 60 and in those with a history of cardiovascular disease. Subsequent to this the authors have been very cautious in their treatment of patients in these categories, keeping them in bed and taking frequent blood pressure readings. However, the element of coincidence in these fatal cases cannot be ruled out, and as time goes on the issue will become clearer.

Liver damage or blood dyscrasias have not so far been a problem. Lehmann *et al.*[8] described jerky tremors in six patients, while English[4] noted three cases of severe generalized tremor which necessitated stopping the drug.

In our series, hypomania, mania and an acute confusional state have proved to be the most serious problems. Patients with early depression, attending as out-patients, may become very distressed if they find themselves in a mental hospital for the first time in their lives. A manic episode in a patient already hospitalized will be far less disturbing and more easily dealt with. However, in patients with no previous history of mania the episodes appear to subside rapidly, especially if treated with large doses of chlorpromazine. The current practice of most mental hospitals is to keep patients for a minimum of several weeks in the event of a hypomanic or manic reaction. Therefore the patient should be treated at home or in a general hospital whenever possible, since the crisis is usually soon past. Another case of mania has been described (Ball and Kiloh[2]) in which the mania did not subside on stopping the drug. There was no history of previous attacks.

Levene and Lascelles[9] reported two cases in which there were signs of overstimulation, e.g. jerky movements, irritability and restlessness, which soon subsided. Brooke and Weatherly[3] described a case of suicidal overdose where the patient became noisy, excitable and aggressive, and attacked two nurses. Another of their patients, who was taking 50 mg. thrice daily, was described as talkative, singing and generally overactive. All these states subsided rapidly on discontinuing the drug. The reason for our comparatively high incidence of manic and hypomanic reactions is obscure. However, our experience is that unless there is a previous history of manic attacks, the natural prognosis is so good that they should not present a serious problem. It is of interest that a recent paper describing the effect of another antidepressant drug, phenelzine, records three cases of mania (Sarwer-Foner *et al.*[12]). Development of rashes led two of our patients to refuse to continue the drug, but Strauss[15] has noted that the rashes can be easily controlled by antihistamine drugs.

We have not discussed the mode of action of the drug, since the biochemical basis is by no means clear and no theory put forward will meet all the facts. It has, in common with iproniazid, nialamid and phenelzine, the property of raising serotonin (5-hydroxytryptamine) levels in the central nervous system. It is not certain, however, that this property is associated with the relief of depression.

SUMMARY AND CONCLUSION

Imipramine is an effective drug in the treatment of endogenous depression and valuable in reactive and psychoneurotic depressions. Severe, suicidal depressions still require electroconvulsive therapy initially. Some patients are resistant to the drug and need electroconvulsive therapy but the majority of patients respond satisfactorily. It would appear to be particularly effective in patients with early depression seen in general practice.

Toxic reactions do occur, but if anticipated so that they can be either prevented or rapidly and effectively treated, they should not prove any bar to use of the drug.

ADDENDUM

Dr. F. B. Stewart, Medical Director of Geigy Pharmaceuticals, writes to us as follows: "We have not been able to demonstrate convincingly that imipramine has the property of raising CNS levels of serotonin, although initially we thought this true. Dr. Brodie of the National Institute of Health in a personal communication stated that he was able to find no effect on serotonin levels with imipramine."

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REVIEW ARTICLE

RECENT ADVANCES IN THE USES OF RADIOACTIVE ISOTOPES IN DIAGNOSIS*

A. H. NEUFELD, M.D., Ph.D.†

TODAY WHEN scientific genius has extended man's intellectual control far beyond the horizons of this planet and when man is at the gate of unleashing the ultimate in power—that residing in the nucleus of the atom, namely its "binding energy"—it somehow does seem apropos that we review the really important item of this story. This has to do with the use of this "binding energy" of the atom in a constructive way for man's health and well-being.

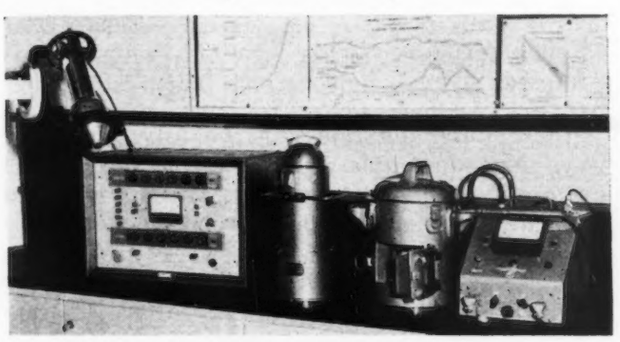

Fig. 1.

We might first take a moment to define an isotope. All chemical elements do have "brother elements", or if you object to this definition, "sister elements". These have identical chemical characteristics of the parent element, but differ in one physical parameter, namely in weight. Usually this difference conveys an instability to these elements so that they tend to break down at a characteristic rate, releasing a certain package of energy in the form of radiation. This can be utilized either as a signal or as a source of energy. I shall restrict my comments to the uses of this emitted radiation as a signal and not as a form of energy for the production of useful work.

In every diagnostic endeavour one should begin with the tools that are involved in the process of diagnosis. In this instance we have merely two tools – the isotope which emits radiation and the unit which is going to receive the "signal" that the isotope has given out.

Three or four relatively simple pieces of equipment (Fig. 1), used in suitable combinations, provide adequate means of performing almost all the clinical tests which have been shown to have diagnostic significance at the present time.

TABLE I.—SOME RADIOISOTOPES USEFUL IN MEDICINE

Name	*Half-life*	*Radiation**	*Energy, mev†*
Arsenic ($_{33}As^{74}$)	17.5 d.	B	0.69, 1.36
		B^+	0.92, 1.53
		y	0.635, 0.596
Bromine ($_{35}Br^{82}$)	36 h.	B	0.46
		y	1.02, 1.29, 1.45
Calcium ($_{20}Ca^{45}$)	163 d.	B	0.256
Calcium ($_{20}Ca^{47}$)	4.5 d.	B	0.66, 1.9
		y	0.50, 0.80, 1.29
Carbon ($_{6}C^{14}$)	5,568 y.	B	0.155
Cesium ($_{55}Cs^{137}$)	33 y.	B	0.52, 1.17
		y	0.66
Cobalt ($_{27}Co^{60}$)	5.24 y.	B	0.312
		y	1.33, 1.17
Gold ($_{79}Au^{198}$)	2.7 d.	B	0.96
		y	0.41
Iodine ($_{53}I^{131}$)	8.1 d.	B	0.61, 0.34, 0.25
		y	0.28, 0.36, 0.64
		y	0.72
Iodine ($_{53}I^{132}$)	2.3 h.	B	1.2, 2.1
		y	0.7, 1.4
Iodine ($_{53}I^{133}$)	21 h.	B	1.25
		y	0.53
Iridium ($_{77}Ir^{192}$)	74 d.	B	0.67
		y (many lines)	0.13-0.61
Iron ($_{26}Fe^{59}$)	45 d.	B	0.45, 0.26
		y	1.3
Mercury ($_{80}Hg^{203}$)	47.9 d.	B	0.21
		y	0.28
Phosphorus ($_{15}P^{32}$)	14.3 d.	B	1.70
Potassium ($_{19}K^{42}$)	12.5 h.	B	1.97, 3.56
		y	1.51
Radium ($_{88}Ra^{226}$)	1,590 y.	The decay products give rise to 12 principal gamma rays with energies ranging from 0.18 to 2.2 mev.	
Radon ($_{86}Rn^{222}$)	3.83 d.		
Strontium ($_{38}Sr^{85}$)	65 d.	y	0.513
Strontium ($_{38}Sr^{89}$)	53 d.	B	1.463
		y	0.913
Sodium ($_{11}Na^{24}$)	15 h.	B	1.39
		y	1.37, 2.75
Sulphur ($_{16}S^{35}$)	87 d.	B	0.167
Thulium ($_{69}Tm^{170}$)	127 d.	B	0.97, 0.88
		y	0.080
Tritium ($_{1}H^{3}$)	12.3 y.	B	0.018
Tantalum ($_{73}Ta^{182}$)	111 d.	B	0.5
		y	0.066 to 1.23

*Beta rays are indicated by B, positrons by B^+, and gamma rays by y. Not all the radiations of these isotopes are indicated, nor are daughters separately designated.

†In the case of beta rays, the energy indicated is the maximum of a continuous spectrum.

It is important to recognize that there are several factors which limit the use of radioactive isotopes in medical practice. The chemistry, pharmacology, metabolic behaviour and radiation spectrum of the element must be known and thoroughly understood. Some of the isotopes useful in medicine and their energy characteristics are listed in Table I.

In a brief communication such as this, one can only give some of the principles underlying the diagnostic applications of procedures and a few illustrative examples. Technological advances are so rapid that the diagnostic applications have as their limiting factor only the inventiveness of the physician. At times, in fact, the boundaries between thoroughly accepted diagnostic procedures and those still in the investigative stage become ill defined. This results from the rapidity of development of new techniques which impose an obsolescence on the already established ones.[1]

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TABLE II.—DIAGNOSTIC USES OF RADIOACTIVE ISOTOPES

Isotope	*Half-life*	*Radiation*	*Use*
Iodine[131]	8 d.	B^-, y	Thyroid uptake and excretion
			PBI[131] and conversion ratio
			Thyroid scanning and mapping
			Plasma and blood volumes
			Liver, kidney function
			Cardiac output
			Fat absorption and digestion
			Tumour localization
Chromium[51]	26 d.	K, y	RBC mass and survival
			Blood loss by bleeding
Iron[59]	45 d.	B^-, y	Iron turnover rate
			Clearance rate from plasma
Iron[52]	8 h.	K, B^+, y	(Serial tests)
Sodium[24]	15 h.	B^-, y	Na space, cardiac output
Sodium[22]	2.6 y.	B^+, y	Na space
Potassium[42]	12 h.	B^-, y	Body "pools"
Phosphorus[32]	14 d.	B^-	Blood volume
			Tumours of eye, skin, cervix
Cobalt[60]	5.2 y.	B^-, y	Pernicious anæmia
Cobalt[58]	72 d.	B^+, y	Pernicious anæmia
Calcium[47]	4.5 d.	B^-, y	Bone lesion localization
Strontium[85]	65 d.	y	Bone lesion localization
Hydrogen[3]	12.3 y.	B^-	Total body water
Arsenic[74]	17.5 d.	B^+, B^-, y	Brain tumour localization

Up to the present time in all diagnostic procedures, one introduces a defined quantity of an isotope into the tissues and then proceeds with observations. Examples are given in Table II. This is known as the "tracer technique". There is much work now in progress on a second technique by "activation analyses" based on production of an isotope *in situ* in a given tissue.[2, 3] Here one activates a desired stable elemental constituent of the body or tissue into a radiation-emitting state and determines its location and quantity by means of suitable radiation-sensing devices. In practice, however, this latter procedure is not yet feasible, for two reasons: firstly, the radiation dosages are such that pathological changes will accrue and, secondly, most elemental constituents amenable to such analysis are too mobile *in vivo* for such approaches.

A good deal of the existing radioisotope technology has been evolved through early applications to the unique, relatively "clean" study of thyroid function utilizing iodine-131. Certainly more sample measurements have been made on this problem than on any other single one, all based on the particular affinity of this gland for the element iodine which it incorporates into its specific hormone. The ideal effects of carrier-free oral tracer intake in the human are illustrated in Fig. 2. This is also an excellent illustration of the information procurable by the "tracer technique", namely the answer to three basic questions:

1. Where does the tracer go?
2. How fast does it go?
3. How much is going?

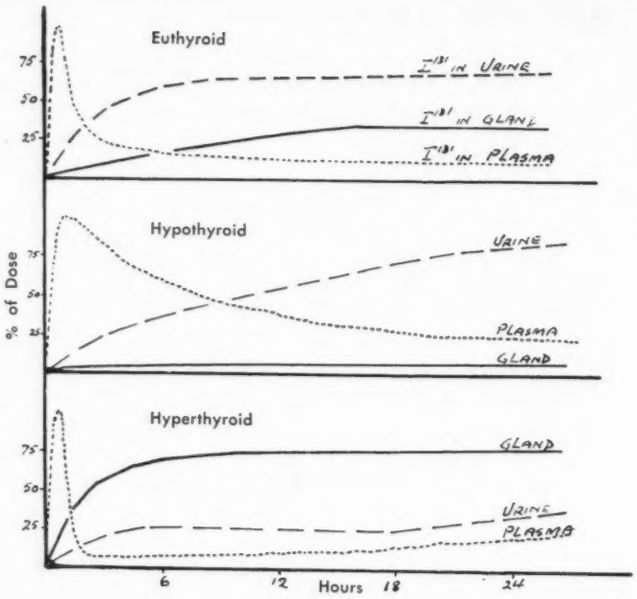


Fig. 2.—Carrier-free oral I^{131} tracer.

These three questions can be asked in many ways depending upon the general areas in which diagnostic aid might be sought. This I will try to illustrate with examples based upon the techniques employed.

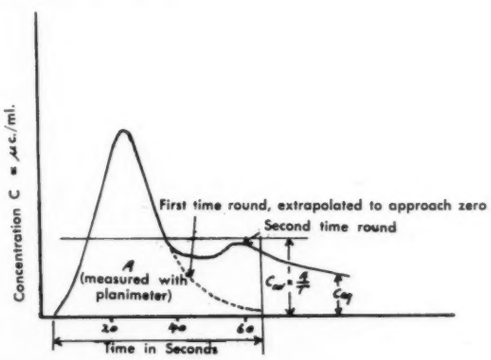
DILUTION TECHNIQUES

Second only to thyroid studies has been the application of radioactive isotopes to the study of the vascular system and to body space. We make use of the technique of "isotope dilution" by tagging and sampling the medium. This permits simple calculation of volumes and masses. However, because of the complexity of the biological system, the method and degree of tagging and the efficiency of the tag component to distribute itself may lead to different "volumes" being measured than are actually intended. For example, large fractions may be "exchangeable" and still others may be accessible only through complex "compartment" interactions. For these reasons, no "volumes" in nature could be more difficult to determine than the "circulating plasma volume" or the "water space" in a patient. Nevertheless, the "volumes" actually measured by the techniques are found to possess a high correlation with numerous clinical criteria and provide one of our most powerful diagnostic tools.

With development of the technique for tagging, more than one isotope may be used concomitantly since the pulse-height analyzers are capable of sorting out specific radiations. It thus becomes possible to measure in the intact man such parameters as total body water,[4, 5] total exchangeable sodium,[6] total exchangeable potassium,[6] chloride space,[5] blood and plasma volumes[7] and others of diagnostic importance.

FLOW RATE TECHNIQUES

These procedures make use of the change of a given quantity of radiation in a given locus per unit time. For example, the measurement of the blood output of the heart is a dynamic measurement of increasing diagnostic use. Its proponents intend it to replace or supplement the arterial puncture technique.[8] As in other studies, all aspects of the physical measurement must be considered. In addition the diagnostic burden is high. The pertinent data appear not only as a mean rate, but also in the form of a transient "bolus". A carefully reproduced result from such a study is shown in Fig. 3. It is obvious, and also evident from this, that the transient to be measured quantitatively occurs in periods of seconds. It is essential, therefore, that the system and recording device have small response times compared to this value. If the system for handling data is slower than these values, then the curve produced will lag behind the actual data and fall short of the appropriate upper value. I might mention that this measurement was made by very careful columation and screening over the aorta.



Injected activity = heart output during
$T \times C_{av}$ = Total blood Volume × Ceq
Flow Rate $= T \times C_{av} = V \times Ceq$
Flow Rate $= \frac{Ceq \times V}{Cav\ T}$ litres/min.

Fig. 3.—Cardiac output with I^{131} human serum albumin.

Iodopyracet (Diodrast) has been in use for assessment of kidney function for many years. The biochemical techniques are cumbersome and elaborate. Radio-opaque modifications have been used for urographic visualization. Recently, radioiodinated Diodrast has become available, permitting the *in vivo* counting studies of instantaneous function.[9] The technique is a dynamic one and makes use of the bilateral symmetry of the body, using one kidney as a reference for the other (Fig. 4). Interpretation of the results of any individual measurement must be based on previous clinical experience with normal measurements. The results indicate three general phases: first, the vascular segment or fast initial response due to distribution of the radioactivity; second, the secretory segment due to the concentration and secretion of the kidney tubules; and third, the excretory segment where elimination is occurring from the kidney to the urinary bladder. Diagnostic information can be gained from the time, absolute magnitude and slope of these different phases.

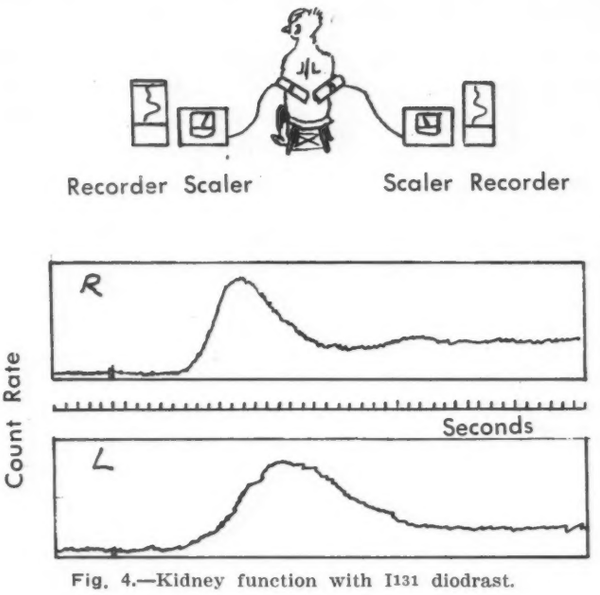


Fig. 4.—Kidney function with I^{131} diodrast.

Similar approaches have been used in measuring the cerebral blood flow in the intact human being,[10] in tests of liver function,[9] and in other measurements which utilize the blood flow as the vehicle for distribution of the tag.

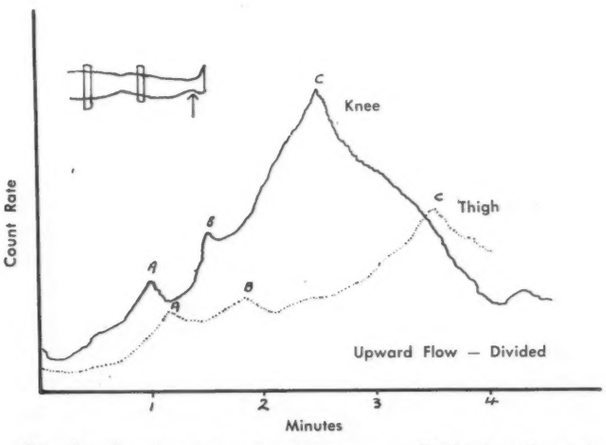


Fig. 5.—Count rate versus time curve. Patient with varicose veins, supine position (after L.T. Cotton *et al.*).

One recent development that deserves more than casual reference is that now in progress on blood flow studies in varicose veins by means of radioactive isotopes.[15] These studies (illustrated in Fig. 5) have shown that the flow of blood in these veins can be followed more satisfactorily by means of a radioactive isotope than by the radio-opaque media which have previously been used. So long as the specific gravity of the tracer injection is modified to that of venous blood, it can be assumed with confidence that the flow of isotope accurately reflects the flow of blood in the vein.

Canad. M. A. J.
Oct. 8, 1960, vol. 83

TUMOUR DIAGNOSIS

The application of the radioisotope techniques to tumour diagnosis is based on the premise that, since a tumour is obviously metabolically different from normal tissues, its affinity for some tracers might also be different. This affinity might be on the positive or on the negative side. The response by enrichment has been utilized extensively and is aided greatly by various scanning methods. The gamma-ray[11-13] and the positron-scanning[14] techniques are among the most popular. The best known example is the localization of metastatic thyroid cancer after administration of I^{131}.

Quite recently considerable interest has been shown in another radioisotope of iodine, namely I^{124}, which emits a positron and has a half-life of 4.2 days.[16, 17] The isotope offers an advantage in the localization of functioning metastatic deposits of carcinoma of the thyroid because the annihilation radiation enables coincidence counting to be used in conjunction with a mechanical scanning technique. This results in much improved spatial resolution. However, relatively large doses of this isotope are necessary and this may limit the value of the coincidence counting.

The chief advantage of iodine-124 lies in the higher energy of its positrons as compared with the electrons emitted by iodine-131. This will lead to a much more uniform dose distribution.

Arsenic-74, copper-64, manganese-52 and potassium-42 have all been utilized in the same manner. Extensive work has been carried out on the presence and location of brain tumours, and the diagnosis of eye and skin tumours and of other tumours.[14, 18]

METABOLIC DISTURBANCES

The field of isotopic diagnosis of metabolic disturbances is the most rapidly expanding and the potential applications are so enormous that only the slightest glimpse of this development can be given here.

The most popular is the use of iodine-131 in the study of thyroid disease. A word of caution on the interpretation of thyroid measurements is in order. All diagnostic procedures will show varying and often invalidating dependence on any previous administration of thyroid-affecting or iodine-containing compounds.

Most of the techniques reported provide reasonably good differentiation between the normal and the hyperthyroid states, as seen in Fig. 6, which is based on analysis of several hundred recordings. There is, however, least clear differentiation between the reduced and the normal gland function. Much effort is therefore being expended in search of techniques to aid the diagnostician in this problem. Thode and his associates measured the I^{131} activity of saliva and related this to the plasma protein-bound I^{131} or plasma total I^{131}. Their results are shown in Table III and indicate the widest

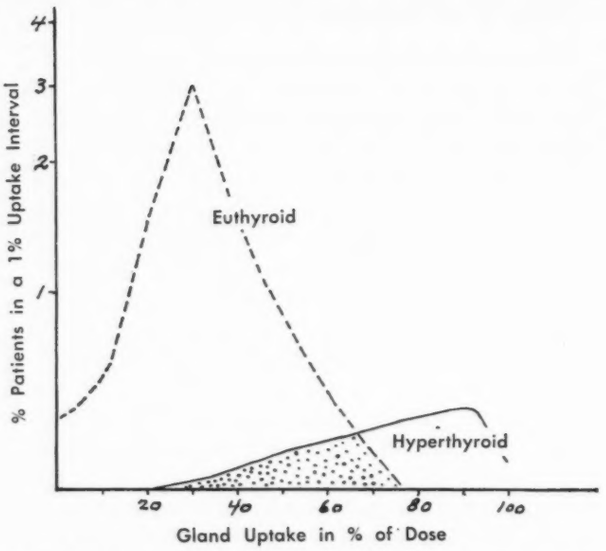


Fig. 6.—Frequency distribution. Critical diagnostic value —61%; diagnostic error—7%.

dynamic range.[19] This or some other approach may prove especially useful in hypothyroid diagnosis.

The radioisotopes have become one of the most essential diagnostic tools for the hæmatologist. Radioactive iron for the study of hæme and hæmoglobin metabolism helps him with problems in regard to the various anæmias, while vitamin B_{12} labelled with radioactive cobalt will establish or rule out pernicious anæmia in patients with gastric anacidity who might already have been treated with liver or vitamin B_{12} for a macrocytic anæmia. Radioactive chromium labelling gives him the opportunity to establish the average survival time, and, with some extension of the test, he can establish whether a decreased survival time may be due to intrinsic defects or whether the red cells are normal but have a short life owing to environmental factors in the patient's plasma. More recently, iron-52, with a half-life of eight hours, has been utilized. It permits serial tests and also more efficient localization studies.

TABLE III.—SALIVARY I^{131} AFTER ORAL I^{131} INTAKE (THODE ET AL.)

	Salivary I^{131}/plasma PBI^{131}
Hyperthyroid	0.25—40
Euthyroid	160—235
Hypothyroid	338-3200

In the study of metabolic functions and aberrations, the fate of the tag can be followed not only in terms of quantity, time, and location, but also in terms of its conversion from one chemical form to another. It is investigation with the aid of carbon-14 and hydrogen-3 tagged organic substances that has elucidated for us normal and pathological metabolic mechanisms involved in carbohydrate, lipid, protein, cholesterol, pigment and other syntheses and breakdowns in the intact body.[5]

These and many other applications of isotopes in the diagnosis and study of metabolic aberrations

render this important area inaccessible to extensive review here, since it is not possible to deal with the isotopic applications without discussing the metabolic pathways in question as well. Therefore, only one application will be dealt with in more detail, one that we have found extremely valuable for an older hospital population as found in a veterans' hospital, namely a simple test to establish the presence and the extent of gastro-intestinal malabsorption.

TEST FOR GASTRO-INTESTINAL ABSORPTION

It has been established in the last 15 or 20 years that intestinal malabsorption occurs in such conditions as sprue, regional ileitis, ulcerative colitis and pancreatic disease, and after surgical operations such as gastric resection. Often the basic underlying etiology will remain unknown, and only secondary manifestations such as weight loss, chronic fatigue, anæmia and other basic nutritional disturbances will be in evidence. This has been largely owing to lack of reliable and simple tests. Determination of the presence and extent of malabsorption was by the metabolic balance techniques. These do not lend themselves readily to clinical use, since they are time-consuming and cumbersome, and require a nursing staff and laboratory facilities which are not always available.

It has been shown that I^{131} labelled neutral fats given orally to normal subjects are transported across the intestinal mucosa and into the blood stream in the same way as ordinary dietary fats.[20, 21] This provides a simple clinical measure of fat absorption, as illustrated in Fig. 7. In normal subjects, the peak blood level of radioactivity is about three hours after administration of the dose and represents approximately 14 to 15% of it. Most I^{131} excretion is by way of the kidneys, 3 or 4% being excreted in the fæces over a three to four day period. In patients with gastro-intestinal disease, blood levels of radioactivity rise slowly and reach a peak level of only 4 to 7%. Fæcal excretion of more than 7% of the administered dose is indicative of steatorrhœa. It is common in these patients to have fæcal excretion of 60 to 70% of the dose.

If a patient has an absorption defect, as indicated by this test, a differential diagnosis may be made by repeating the procedure but this time using I^{131} labelled oleic acid. Patients with pancreatic insufficiency cannot absorb neutral fat such as triolein, since there is a deficiency of pancreatic lipase, which is necessary for hydrolysis and subsequent absorption of the hydrolysed fat through the intestinal wall. Oleic acid is absorbed through the intestinal wall directly without the necessity of prior hydrolysis.

Blood levels of radioactivity after administration of oleic acid will be normal in those patients whose absorption defect is due to pancreatic insufficiency, such as pancreatitis, carcinoma, or blockage of the pancreatic ducts. If absorption of both triolein and oleic acid is low, the patient may be diagnosed as having sprue or a related disorder.

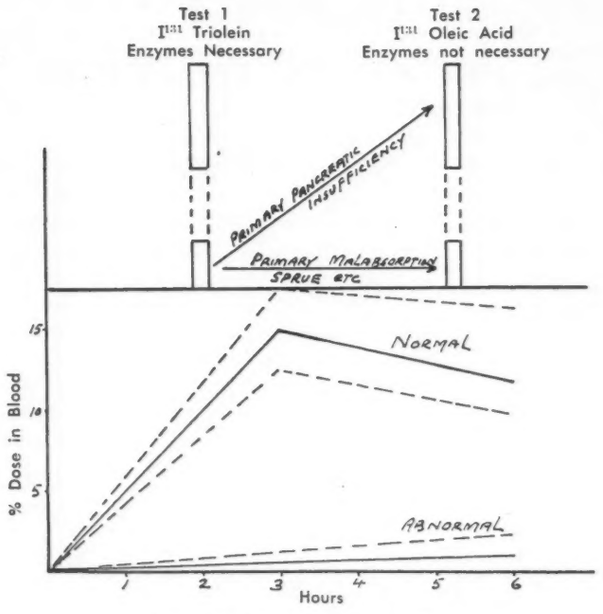


Fig. 7.—Fat absorption test.

As a final note, much has been said and written on multiplication of sources of radioactive contamination during the last two decades. These may lead to possible contamination of water, of food-producing resources and food supplies, which can lead to internal contamination in man. I do not believe that the infinitesimally small amounts of "relatively safe" radioisotopes that are used today in diagnosis and in medical research contribute in any way to the so-called "world contamination" problem.

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Canad. M. A. J.
Oct. 8, 1960, vol. 83

MEDICAL ECONOMICS

SWIFT CURRENT, TWELVE YEARS LATER

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THE PROPOSALS of the Government of Saskatchewan to institute a province-wide tax-supported medical services plan for the whole population has focused attention on the system which has been operative in Health Region No. 1 since 1946. The Swift Current Medical Care Program remains the only Canadian example of a compulsory, publicly financed system of medical care insurance covering the entire population of a large area, and it is pertinent to re-examine it in the light of current developments.

As a baseline of reference it is proposed to compare the fact and opinion expressed in an article published 12 years ago[1] with data from the annual reports of the original administrator who continues to occupy the appointment of Secretary-Treasurer of Health Region No. 1.

The population at risk in the Region is only slightly greater than it was in 1948, in round figures 50,000 men, women and children. Physicians now number 41 compared to 34 in 1948, but one gathers the impression that the representatives of the profession have been very mobile and that the tenure of individual doctors has been brief.

The scope of service rendered under the plan continues to be comprehensive, with specialist services beyond the resources of the Region obtained by referral.

In 1948 two certificated specialists were engaged in clinical practice and one specialist in radiology was stationed at the Swift Current General Hospital; today there are eight specialists at work in the Region.

It is axiomatic that the utilization of services by a fully insured population will be at a rate higher than that which would otherwise apply and in Health Region No. 1 this is demonstrated. Tables published in the 1959 report of the Saskatchewan Hospital Services Plan show Selected Primary Surgical Operations per 1000 persons covered to be in excess of 50 in the Region against a provincial average of 39. Discharges from hospital show a similarly high rate of utilization. It was to be expected that stabilization of demand for medical services might be achieved in such a situation after the passage of a few years. In the Swift Current Region this is not yet evident, or at least the plateau which has been established is sufficiently high to distinguish the service provided from that of other areas of the province.

In an effort to conserve funds and to impose some restraint on utilization, effective January 1, 1953, the Plan instituted a limitation on its payment for home calls of $2.00 for ordinary calls and $3.00 for emergency calls. In August of that year a limitation of the Plan's liability for ordinary office calls to $1.00 was applied, with $2.00 payable by the Plan for office visits where a complete physical examination was carried out. The subscribers are responsible for the payment of the difference between the appropriate medical fees and the allowances provided by the fund.

In effect, this constituted a deterrent fee and introduced an element of co-insurance which was not previously applicable. Like most deterrents, this one effected a prompt reduction in the demand for these categories of service but in the intervening years both office and home calls have gradually assumed their previous levels.

The financing of the Swift Current Medical Care Program continues to be based on a personal tax and a property tax supplemented by a provincial grant. The rates of taxation and the revenues derived are set out in the appended table which includes the latest year (1958) for which a full report is available.

During the period under discussion several changes have been made in the rates of remuneration of physicians, in the method of providing diagnostic services and in the scope of procedures available to doctors and patients. For example, at the inception of the Plan the remuneration of Regional physicians was based on fee-for-service at 75% of the 1938 Schedule of the College of Physicians and Surgeons; in 1958 at 75% of the 1956 Schedule, and the current basis of payment is 80% of the 1959 Schedule. In 1952 payments from

Revenue	*1947*		*1958*
Personal tax			
(a) Single individual	$ 10.00		$ 19.00
(b) Family of two	20.00		31.00
(c) Family of three or more	30.00		40.00 - 48.00
Total revenue from these sources	376,012.00		619,385.00
Property tax—2 mills on assessed value	139,000.00	Average 2.4 mills	209,206.00
Provincial grants	76,537.00		69,839.00
Sundry revenue	1,390.00		12,880.00
Total	$592,939.00		$911,310.00
Expenditure			
Medical Services			
(a) Within the region	$401,453.00		$633,623.00
(b) Outside the region	58,547.00		82,116.00
	$460,000.00		$715,739.00
Outpatient services	50,000.00		69,499.00
Dental services	40,697.00		55,103.00
Radiological services (Regional)	11,177.00		26,140.00
Administration	23,570.00		44,332.00
Commission to municipalities for tax collection	15,000.00		24,401.00
Total	$600,444.00		$935,214.00

the pooled fund for diagnostic procedures performed in physicians' offices were, with a few exceptions, discontinued and these services were provided as hospital outpatients' benefits.

The average gross income from the Plan of the 34 participating Regional physicians was reported in 1948 as $11,807. In 1958 the comparable figure for the 41 Regional doctors was $15,454. The Plan continues to be administered by an autonomous, elected, Regional Board on which the participating physicians are not represented. The Medical Advisory Committee, however, has been active and it has been effective in negotiating changes and improvements in line with the profession's viewpoint.

It has been said by Douglas Robb in his appraisal of the New Zealand Medical Services[2, 3] that the impact on medical research and education has been negligible, that emphasis is almost exclusively on service and that the planners were unable or unwilling to include any serious concern for quality. The same observation might be made of the Swift Current Medical Care Program, which is now, as it was originally designed to be, a device for prepayment of the costs of personal medical services. It has, however, survived and in the period since 1946 has adjusted to many factors which would have wrecked a plan which had less public and professional support.

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Case Reports

BUDD-CHIARI SYNDROME

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OCCLUSION of the hepatic veins is rare, but its clinical recognition is important. The clinical syndrome resulting from occlusion of the hepatic veins was originally mentioned by Budd in 1846; it was associated with thrombosis of these vessels complicating liver abscess. Chiari, in 1899, more fully outlined the clinical and clinico-pathological correlations of the malady and associated it with primary obliterative endophlebitis which usually began in the larger radicles of the hepatic veins and often extended to the inferior vena cava. The presenting configuration is therefore properly designated as the Budd-Chiari syndrome.

This report was prompted by the rarity of this type of veno-occlusive disease of the liver, and the paucity of ante-mortem diagnoses. The scarcity of reports may in some instances be ascribed to lack of careful dissection of the hepatic veins at post-mortem examination. In the case presented, the correct diagnosis was established during life, but unfortunately a most intensive therapeutic regimen failed to prevent the patient's demise.

P.F., a 37-year-old single white male physician, was admitted to hospital on December 28, 1959, with a ten-day history of vague abdominal distress, bloating, irregularity of bowel movements, shortness of breath, and swelling of the abdomen and legs.

Past history was not obtainable during life. However, recently it was learned that in 1952 he had visited University College Hospital, London, England, because of pain in the left upper quadrant and left shoulder tip. Salient physical findings were mild splenomegaly and palpable liver. Significant laboratory findings were a hæmoglobin value of 123%, red blood cell count (R.B.C.) 6.4 million, platelet count 670,000, hæmatocrit value 55%, and a normal liver profile. No definite diagnosis was made, although splenic vein thrombosis was considered likely. The family history was interesting in that the patient's father had succumbed approximately 15 years previously to bleeding œsophageal varices complicating what was diagnosed as post-hepatitic cirrhosis.

The patient was a well-developed and well-nourished man, obviously uncomfortable and moderately dyspnœic. Temperature and pulse were normal, and blood pressure (B.P.) was 120/80 mm. Hg. He had massive ascites, an enlarged, firm, non-tender liver with a rounded edge, splenomegaly, prominent periumbilical and lateral thoracic veins bilaterally, and pitting œdema of the lower limbs to the knees. There was no evidence of jaundice or jugular venous distension. His cardiovascular status was normal and the chest fluoroscopy revealed nothing remarkable.

Laboratory Findings

Urine.—Normal on admission; specific gravity was 1.030. During the course of the illness, his urine contained 1-2 + bile and 3-4 + urobilinogen.

Hæmatological values.—R.B.C. 8,000,000; hæmoglobin 19.4 g. (124%); W.B.C. 14,900 and normal differential count; platelet count 448,000 (large and bizarre); reticulocytes 2.2%; hæmatocrit 60%. M.C.H. was 24; M.C.V., 81; M.C.H.C., 30%. Sedimentation rate was 5 mm. in one hour. Total blood volume was 7560 c.c., total red cell volume 4919 c.c., and total plasma volume 2646 c.c.

Blood chemistry.—Liver profile: serum bilirubin 1.8 mg. % (on admission); serum bilirubin (January 19, 1960) 8.3 mg. %; cephalin-cholesterol flocculation 3 plus; thymol turbidity 4; bromsulphalein 20% retention in 45 minutes (5 mg. per kg.); prothrombin time normal; serum transaminase 106 units; total protein 6.8 g.; albumin 4.8 g. and globulin 1.98 g. Electrophoretic strip: albumin 53; α_1 globulin 15, α_2 globulin 27, β globulin 19, and γ globulin 16.

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Canad. M. A. J.
Oct. 8, 1960, vol. 83

ELECTROLYTE STUDIES

	24-hour urinary excretion				*Serum electrolytes*			
Date	*Volume ml.*	*Na mEq./l.*	*Cl mEq./l.*	*K mEq./l.*	*Na mEq./l.*	*Cl mEq./l.*	*K mEq./l.*	*Remarks*
Dec. 29/59	610				141	111	5.3	
" 31/59	580							
Jan. 1/60	420							
" 2/60	285							Prednisone and chlorothiazide started
" 3/60	250							
" 4/60	500				136	107	5.4	
" 5/60	600							
" 6/60	650							
" 7/60	725							Spironolactone started
" 9/60	1340	4.3	6.7	37.1				
" 10/60	2050	7.9	6.7	78.3				
" 11/60	840				130	82	4.3	
" 12/60	1600	40.3	4.1	99.0				
" 13/60	2160	77.8	8.1	49.2				
" 14/60	3550	118.0	7.6	22.8				
" 15/60	2750							
" 16/60	2050							
" 17/60	980							
" 18/60	1000	22.0	6.3	36.1				
" 19/60	1050	24.3	6.6	52.5	127	72.9	3.8	Spironolactone stopped
" 20/60	1150							
" 21/60	1290							
" 23/60	1200							
" 24/60	1300							
" 25/60	1410							
" 26/60	1260				130	92.7	4.9	

Miscellaneous.—Blood sugar and non-protein nitrogen values were normal. Serum amylase level was normal. Uric acid was 5.2 mg. %, and total cholesterol 170 mg. %. A blood Wassermann test was negative. Stools were positive for occult blood, while culture results were negative. An electrocardiogram was within normal limits.

Examination of ascitic fluid.—Turbid straw colour; protein value was 2.18; total cell count, 573; and differential count, neutrophils 3, lymphocytes 86, stab forms 4, monocytes 3, and eosinophils 4. Exfoliative cytological examination was negative for malignant cells. Acid-fast bacilli were not detected and routine cultures were negative in results.

X-ray studies.—Normal intravenous pyelogram (I.V.P.), chest, barium enema, stomach and small bowel series. Varices of the œsophagus were disclosed.

Diagnosis

1. Budd-Chiari syndrome
2. Polycythæmia vera
3. The veno-occlusive disease of the liver may be related to pre-existing chronic hepatitis or to an undetermined mechanism, possibly associated with polycythæmia.

Hospital Course and Management

On admission, the patient was given a high carbohydrate, salt-free, low protein diet, mercaptomerin (Thiomerin), crude liver extract intramuscularly, and supplementary vitamins. Although his œdema cleared promptly, the ascites continued to recur rapidly, necessitating removal of three to four litres at intervals of four to six days. Because of the polycythæmia, the patient was subjected to five venesections of 400 c.c. each, with relatively little effect on the hæmogram.

Because of failure to obtain a diuresis, on January 2, 1960, prednisone and chlorothiazide were added. These had no immediate effect and on January 5, the chlorothiazide was discontinued. On January 7, spironolactone (Aldactone) was added to the regimen. With this therapy, diuresis was achieved, with temporary alleviation of his ascites, but this effect was soon lost.

On January 16, the patient rapidly went into progressively deep coma, from which he never recovered. At this time his nutrition was maintained by the parenteral route and consisted of 5-10% glucose in water, supplementary vitamins; intravenous glutamate, hydrocortisone (Solu-Cortef) and tetracycline and Durabolin administered intramuscularly. During the first 48 hours of his comatose state, enemas and purgatives were administered as well as a course of neomycin by duodenal tube. After an interval of ten days, the veins proved to be unsatisfactory for further alimentation and it was then achieved by duodenal tube. Electrolytes were replaced as necessary.

The patient died on the thirty-third hospital day after a profuse episode of hæmatemesis, approximately 43 days after onset of symptoms.

Post-Mortem Findings

Gross description.—The body was that of a man appearing his stated age of 37 years, weighing 120 lb. and 5 ft. 6 in. in height. There were petechial and ecchymotic hæmorrhages over the forearms and marked distension of the superficial veins of the arms. There was slight jaundice. The brain weighed 1510 g. and appeared œdematous. The thyroid weighed 10 g., being small and firm but showing colloid on cut surface. Right lung weighed 775 g. and left lung 590 g. All lobes were markedly congested and œdematous.

Heart weighed 300 g. Atria and myocardium were normal. Left coronary artery was atherosclerotic at the division into circumflex and anterior descending

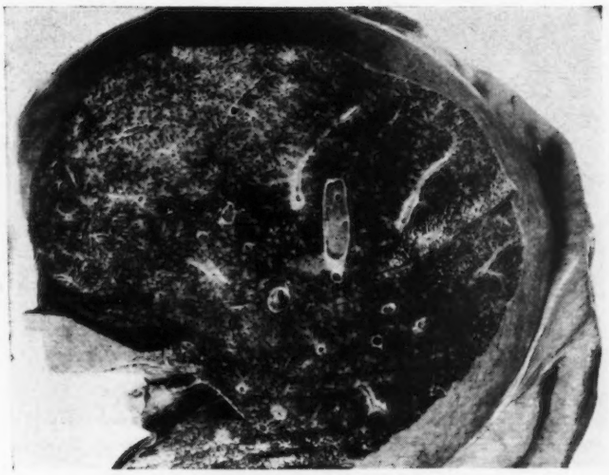

Fig. 1.—Cut surface of liver—chronic passive congestion.

branches. Aorta was slightly atheromatous in the region of the aortic valves but was otherwise free of atheroma, though bile-staining of the intima was present.

After removal of the thoracic viscera the intercostal and azygos veins were seen to be very distended. The peritoneal cavity contained 3500 c.c. of straw-coloured fluid. Numerous peritoneal adhesions were present, particularly around the spleen, which was adherent to the omentum and diaphragm. The omental veins were very tortuous and dilated, but there was no apparent dilatation of the veins of the abdominal wall.

Œsophagus was congested and inflamed, and immediately above the cardia there was tortuosity and

Fig. 2.—Inferior vena cava and hepatic veins — fibrous occlusion of hepatic veins.

Fig. 3.—Hepatic vein—stenosis behind orifice of vein into inferior vena cava.

prominence of the veins and superficial mucosal erosion. Stomach contained altered blood and in the mucosa numerous petechial hæmorrhages and ecchymoses were seen. Similar submucosal hæmorrhages and petechiæ were seen throughout the whole length of the colon and rectum.

Liver weighed 2000 g. and the right lobe appeared large, the left being small and somewhat flattened. The surface was smooth and mottled, with dark purple and brown-yellow areas. Cut surface revealed marked mottling with dark purple-brown areas and bright yellow tissue between them, the appearance being that of a gross "nutmeg" liver. Inferior vena cava was of normal size, but had a few tiny intimal tags near the hepatic veins. Hepatic veins were grossly abnormal. Only one vein of any size was patent, the orifice being approximately 1 cm. in diameter. On opening this it was seen to be stenosing immediately behind the orifice, causing further reduction of the lumen, but beyond the stenosis it was markedly dilated. The stenosis was concentric and produced puckering of the intima, though distally and proximally the intima was smooth. Openings of the other hepatic veins were completely occluded by dense fibrous tissue involving a segment about 0.5 to 1 cm. in length. Beyond the obstruction the vein was smooth and extremely dilated. A few patent tiny veins that arose mainly from the capsular region of the liver opened into the inferior vena cava. None of the vessels were thrombosed. The portal vein and its main tributaries were of normal calibre, and the hepatic artery was normal.

Canad. M. A. J.
Oct. 8, 1960, vol. 83

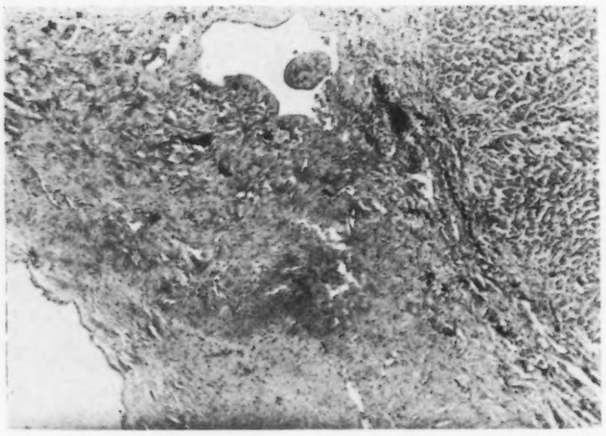

Fig. 4.—Hepatic vein (H. & E., × 40 approx.). Stenotic area, subintimal fibrosis.

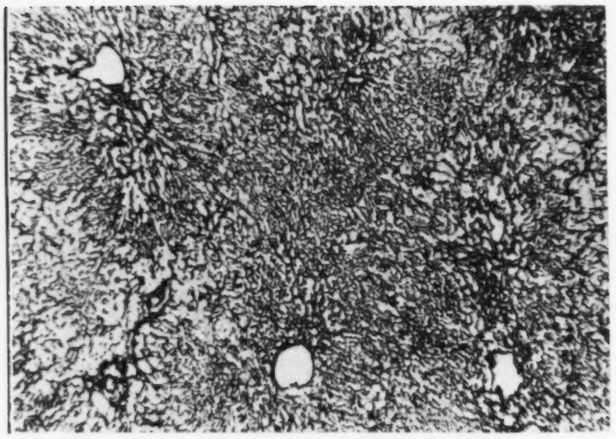

Fig. 5.—Liver, reticulin × 40. Intact reticular pattern in congested areas.

The gallbladder was rather thick-walled and contained thick viscid bile. Spleen weighed 500 g. and the surface was covered with adhesions. It was firm and on cut surface showed uniform purple tissue. Two small infarcts were present. Pancreas weighed 140 g. and appeared normal. Right adrenal weighed 7 g. and the left 11 g., and they appeared normal. Right kidney weighed 212 g. and the left 200 g.; there was marked congestion. Ureters, bladder, prostate and testes were unremarkable. Lymph nodes were not enlarged.

Microscopic description.—Lungs showed focal areas of bronchopneumonia, focal hæmorrhage and œdema.

Sections of liver revealed marked centrilobular congestion with necrosis of the central and mid-zone parenchymal cells, leaving only a rim of apparently normal cells in the portal areas. The reticulin framework of the lobules was intact. One section of the liver contained fibrosis in the portal areas and increased lymphocytic infiltration and some nodules of regenerating liver cells. Here the portal tracts connected with one another, but elsewhere in the liver there was no apparent portal fibrosis or regenerating liver nodules. Section of the stenosing hepatic vein showed a focal area of marked subendothelial fibrosis containing many reticulin fibres. Only fibroblasts and a few capillary vessels were seen and there was no inflammatory reaction.

Section of the occluded vein revealed only a dense nodule of fibrous tissue and hyalinized collagen fibres. The wall of the inferior vena cava in this region showed similar subendothelial fibrosis. Underlying liver tissue was similar in appearance to that seen in the congested areas.

The spleen was congested and showed markedly dilated prominent sinusoids and some increase in number and thickness of the fibrous tissue septa. No extra-medullary hæmopoiesis was found. Sections of bone marrow showed marrow cavity of the vertebral body to be filled with apparently active hæmopoietic tissue. Sections of all other organs were within normal limits.

Final pathological diagnosis.— Subendothelial fibrosis of hepatic veins, with stenosis and occlusion (Budd-Chiari syndrome).

ETIOLOGY

Although many causes for this syndrome have been postulated, few have been proved. It usually results from chronic inflammatory disease, migratory phlebitis or neoplasm. The etiological circumstances leading to occlusion of hepatic veins may be conveniently classified as follows:

A. Intrahepatic—leading to stricture or compression of hepatic veins.

1. Primary obliterative endophlebitis of the hepatic veins or their ostia.

2. Chronic hepatitis (viral and parasitic), cirrhosis.

3. Cholangitis and liver abscess.

4. Tumours—primary and metastatic.

5. Bush tea poisoning.

B. Extrahepatic

1. Compression of hepatic veins by cysts, abscess, tumour or perihepatitis.

2. Thrombosis or stenosis of the inferior vena cava at the ostia of the hepatic veins. Intraluminal extension of tumour.

3. Thrombophlebitis migrans.

4. Extension of portal vein thrombosis.

5. Blood dyscrasias: polycythæmia vera, myeloid leukæmia, sickle cell anæmia. (Cases of Budd-Chiari syndrome have been reported in association with polycythæmia vera, although the hepatic veins are rare sites of thrombosis in this disease.)

PATHOGENESIS

The liver possesses a double blood supply via the hepatic artery and portal vein, with free mixing of blood in the sinusoids, and drainage of both systems by a common venous return, through the hepatic veins. The latter originate as central veins of the hepatic lobules and drain into the inferior vena cava. They are valveless and lack a vessel sheath and are therefore liable to obstruction and invasion by infection or tumour. They may be obstructed centrally (e.g. congestive failure) or peripherally. This highly vascular organ depends for its major oxygen supply on the relatively low pressure, poorly saturated, portal venous blood. The central cells of the anatomical lobule, being farthest from the source of supply, are in a precarious position and first to suffer from anoxia.

Several theories have been postulated that suggest mechanisms which may predispose to occlusion of the hepatic veins. These include:

1. Congenital anomalies of the hepatic veins.
2. Obliquity of the juncture of the hepatic veins with the inferior vena cava.
3. Torsion of the hepatic veins in the upright posture, and
4. Stasis in the inferior vena cava at its diaphragmatic hiatus consequent to elevation of intrathoracic pressure during inspiration.

The site of occlusion is usually at the junction of the hepatic veins with the inferior vena cava. There may be obstruction of the ostia of the hepatic veins or extension of a thrombus from the vena cava along the hepatic veins. Primary occlusion of the veins in the liver substance beyond the inferior vena cava (as in the case reported) is rare. In particular situations bland or septic thrombi may be encountered.

In the light of current concepts, probably a combination of factors plays a role in the production of ascites in this situation, including elevated portal venous pressure, decreased plasma protein colloid osmotic pressure, and renal and hormonal factors related to the effect of antidiuretic hormone and secondary hyperaldosteronism. Experimental studies suggest that the source of the ascitic fluid here may be the hepatic lymphatics as well as the capillaries of the gastro-intestinal tract.

Pathological Findings

The tissue changes in the liver are secondary to mechanical circulatory obstruction, and, depending on the distribution of the affected veins, may be generalized or localized.

The liver is enlarged, smooth and firm. The cut surface exhibits the nutmeg appearance of intense chronic passive congestion and may show areas of hæmorrhage. In more chronic cases, nodular hyperplasia and fibrosis are reported. The main histological features are centrilobular congestion, necrosis and atrophy.

The spleen is enlarged and shows severe venous engorgement and in some instances infarction.

The changes in the veins include endophlebitis and periphlebitis of the hepatic veins and inferior vena cava, intimal plaques, phlebosclerosis and venous thrombi.

Cirrhosis and primary carcinoma of the liver have been found in a significant number of cases of Budd-Chiari syndrome, and it has been suggested that, in some instances, the veno-occlusive disease may be the antecedent circumstance.

Senecio or bush tea poisoning, a special form of veno-occlusive disease of the liver presenting as Budd-Chiari syndrome, is not uncommon in the West Indies and Africa. Many persons in these areas are exposed to a variety of herbs, including senecio weed in wheat fields which may contaminate the flour. Since only a small number of those exposed develop the disease, these are likely not the only causative agents, but may condition the liver to other factors. The tissue changes include necrosis, hæmorrhage, thrombi in the small intrahepatic veins, and absence of liver cell regeneration and fibrosis. The primary site of action of senecio toxin is considered to be the endothelium of the central and lobular veins. It is noteworthy that in these cases the larger hepatic veins or inferior vena cava were not affected, whereas they are in most instances of Budd-Chiari syndrome.

The illness is encountered in all age groups, may be familial, and tends to be severe, with a high mortality.

Clinical Features

The syndrome is encountered in both sexes with equal frequency and may occur at any age, though it is most common between 30 and 40 years.

In the absence of antecedent hepatic enlargement, because of congestive failure, cirrhosis or massive neoplastic involvement, the clinical manifestations of occlusion of the hepatic veins are characteristic. The syndrome may present in one of two forms.

In the acute form resulting from sudden obstruction of the hepatic veins, the prominent features are severe pain over the liver radiating to the back and shoulders, nausea and vomiting, a rapidly enlarging tender liver, splenomegaly and ascites. Fatal hepatic coma may ensue in one to four weeks.

In chronic cases due to gradual venous occlusion or repeated thrombotic episodes, the symptoms and signs include pain in the epigastrium and right upper quadrant, nausea and vomiting, progressive enlargement of the liver and spleen, rapidly accumulating ascites resistant to diuretics, œdema of the lower limbs, and hydrothorax and distension of venous collaterals over the upper abdomen and lower thorax. Jaundice is relatively rare and is mild when present. When the syndrome is secondary to cirrhosis, the liver may be small. Terminal mesenteric venous thrombosis may be accompanied by diarrhœa. The hepato-jugular reflex is absent, indicating obstruction between the hepatic and jugular veins. The collateral circulation develops more frequently in chronic than acute cases.

Laboratory Findings

The liver profile frequently shows relatively little abnormality except for early marked B.S.P. retention.

In other instances hyperglobulinæmia, prolongation of prothrombin time, decrease in the esterified cholesterol fraction, variable bilirubinuria and urobilinogenuria may be encountered. The sedimentation rate tends to be high when the obstruction is due to malignant neoplasm or septic phlebitis. Associated involvement of the renal veins and throm-

bosis of the inferior vena cava may give rise to proteinuria, azotæmia and nephrotic syndrome.

Differential diagnosis includes chronic constrictive pericarditis, portal cirrhosis, portal vein thrombosis, and thrombosis of the inferior vena cava. The acute form must be differentiated from congestive heart failure and early decompensated cirrhosis.

Chronic constrictive pericarditis is characterized by elevated jugular venous pressure, the cardiac findings including the radiological and electrocardiographic changes and the relatively high protein content of the ascitic fluid.

Portal cirrhosis may be suspected from the antecedent history, the gradual onset, the small liver and the evidence of hepatic dysfunction, the ascites usually responding to a medical regimen, at least initially.

Thrombosis of the portal vein may be difficult to differentiate. It rarely causes ascites, and œdema is rare. The pattern of the venous collaterals may provide a helpful clue.

In thrombosis of the inferior vena cava the direction of flow in venous collaterals is cephalad, while in occlusion of hepatic veins it is caudad.

COURSE AND PROGNOSIS

These depend on the cause and the abruptness and severity of the venous occlusion. Fatal termination may be due to hepatic coma, bleeding œsophageal varices, mesenteric thrombosis, or to renal failure in cases where the inferior vena cava and renal vein are involved. Prognosis is almost always poor, with a fatal exitus in one to four weeks in acute cases. Usually hepatic failure with delirium and coma ensues within six months. Subsequent recanalization, development of an adequate collateral circulation through porto-systemic anastomoses, and regeneration of the liver may permit prolonged survival in isolated cases of Budd-Chiari syndrome.

TREATMENT

There is no effective specific therapy. The therapeutic regimen is essentially palliative and supportive, directed toward maintenance of nutrition and the management of complications including ascites, fluid and electrolyte depletion, bleeding varices and hepatic coma. The use of anticoagulants in the few cases where the diagnosis of venous thrombosis is certain, has been suggested, but may not be without danger. Where an infective etiology is the underlying cause, appropriate antibiotic therapy is indicated. The combined use of diuretics, prednisone and an aldosterone antagonist to stem the rapidly recurring ascites has, at least in the case reported, not proved effective.

In chronic cases portacaval shunt has been suggested and tried, usually without spectacular effect. The condition of these patients often does not permit a surgical approach, and because of associated obstruction of the inferior vena cava, such an anastomosis may not be feasible. In some instances, the latter may be determined by saphenous venography. The value of portacaval shunt in ascites resistant to medical therapy, and in the absence of bleeding varices, is doubtful in most instances, and the procedure is considered to be contraindicated by many workers.

SUMMARY

A case of Budd-Chiari syndrome resulting from primary obliterative endophlebitis of the hepatic veins has been reported. The salient pathological and clinical features are reviewed. Some of the therapeutic possibilities in an ominous situation are mentioned.

The author is indebted to Dr. M. J. Cassels, assistant pathologist, New Mount Sinai Hospital, Toronto, for the autopsy findings and illustrations; to Professor J. Dauphinee, Department of Pathological Chemistry, University of Toronto, for the determinations of urinary electrolytes; and to Professor K. J. R. Wightman, Department of Medicine, University of Toronto, for the hæmatological studies.

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Canad. M. A. J.
Oct. 8, 1960, vol. 83

GOUT AS A COMPLICATION OF CHLOROTHIAZIDE THERAPY*

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THE INTRODUCTION of chlorothiazide as a potent oral diuretic and more recently as a potentiator of hypotensive agents has led to its widespread clinical use. In addition to the depletion of body stores of potassium and sodium, it has been noted that chlorothiazide is associated with hyperuricæmia.[1] In certain patients "gout-like" symptoms have appeared.[2, 3] The purpose of this communication is to report a case in which chlorothiazide administration was associated with the onset of attacks of classical gouty arthritis.

The patient, a 78-year-old man, first presented at the out-patient department of the Winnipeg General Hospital in October 1956, complaining of constipation. On examination he was found to have a slight parkinsonian tremor, a calcified thyroid nodule and benign prostatic hypertrophy. His blood pressure was 160/95 mm. Hg, and an aortic systolic murmur was noted. No organic gastrointestinal lesion was demonstrated. A chest radiograph revealed moderate cardiomegaly and increased bronchovascular markings. The blood urea nitrogen (BUN) value was normal. Since the patient was thought to be in incipient congestive heart failure, digitalization was carried out. An occasional mild laxative relieved the patient of constipation.

The patient was reasonably well until September 1958, when he returned with increasing dyspnœa, progressively diminishing effort tolerance, ankle œdema, jugular venous distension and a further increase in heart size. In addition to digitalis he was given a low-salt diet and 500 mg. chlorothiazide daily for three weeks. Near the end of this three-week period he was awakened in the night by severe pain in the right great toe which was red, hot, tumescent and exquisitely tender. Serum uric acid level at this time was 10.2 mg. % (normal range 4.0-6.5 mg. %) (see Fig. 1). After a few days of rest and salicylates the symptoms subsided. During this time the course of chlorothiazide therapy ended.

On April 1, 1959, the patient was again given 500 mg. chlorothiazide daily, and after six weeks he experienced a second attack of gouty arthritis in the right great toe. Serum uric acid level was 7.9 mg. %. Phenylbutazone and probenecid controlled the symptoms, and once again chlorothiazide administration was discontinued. Chlorothiazide, 250 mg. daily, was administered from May 22 to July 20, 1959, when he had a third attack of gout, on this occasion in the left great toe (serum uric acid value 9.9 mg. %). Colchicine relieved the symptoms, and administration of chlorothiazide was discontinued. The serum uric acid level, however, remained elevated. The patient experienced no further episodes of gouty arthritis, but on September 11, 1959, suffered an attack of renal colic and nine days later passed a urate calculus.

*From the Out-Patient Department, Winnipeg General Hospital, and the Faculty of Medicine, University of Manitoba.

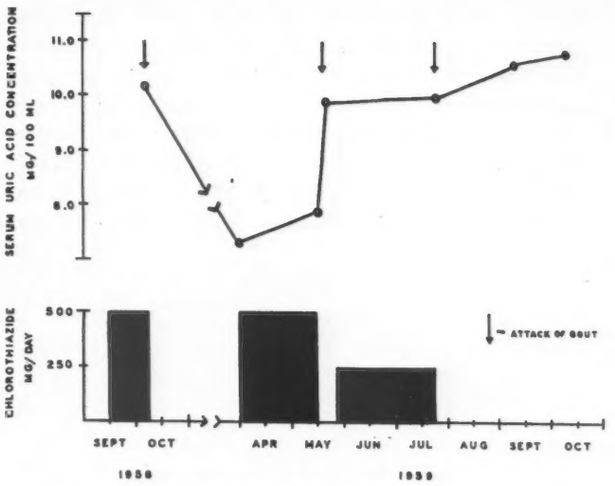

Fig. 1.—The relationship between hyperuricæmia, attacks of gout and chlorothiazide administration in a patient with congestive heart failure.

DISCUSSION

Hyperuricæmia during chlorothiazide administration was first observed by Laragh *et al.*[1] In six of eight patients studied, the serum uric acid level varied from 7.6 to 11.5 mg. %. None of these patients had joint symptoms, and their uric acid fell to normal values promptly when chlorothiazide administration was discontinued.

Oren and Rich[2] observed hyperuricæmia (serum uric acid value 6.3-10 mg. %) in all 12 of their patients receiving chlorothiazide. Three of their patients had joint pains in the feet and one of these had radiographic findings consistent with gout. The latter, however, had had a previous attack of gout, but it is not stated in the report whether or not there was a family history of gout. Similarly, in the case reported by Healey *et al.*[3] attacks of gout antedated administration of chlorothiazide.

In our case the significant features were the relationship between the administration of chlorothiazide and the attacks of gouty arthritis, the absence of previous attacks of gout, the negative family history and the persistently elevated levels of serum uric acid despite cessation of therapy. The first three features suggest that chlorothiazide produced gout in an individual with previously normal uric acid metabolism. The persistence of a high serum uric acid concentration may on the other hand indicate that the patient in fact did have an abnormal uric acid metabolism before chlorothiazide was administered or it may signify a permanent chlorothiazide-induced defect. Either interpretation attributes to chlorothiazide an important effect on uric acid metabolism—on the one hand as a precipitator of gouty arthritis in a susceptible individual and on the other as an agent which may produce gout even in a normal person.

The mechanism by which chlorothiazide produces hyperuricæmia has not been elucidated. It seems likely that it is an effect of the drug on the kidney rather than on nucleic acid metabolism. Healey, Magid and Decker[3] demonstrated a re-

Canad. M. A. J.
Oct. 8, 1960, vol. 83

duced renal clearance of uric acid in patients receiving hydrochlorothiazide. Since glomerular filtration was unaffected, the effect of the drug was considered to be on the renal tubule. Further investigations are necessary to determine whether alterations in tubular absorption or tubular secretion are responsible for the changes in renal clearance of uric acid during administration of chlorothiazide.

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AN UNUSUAL CASE OF ERYTHEMA NODOSUM

NORMAN CARL KERBEL, B.A., M.D., *Toronto*

ERYTHEMA NODOSUM is an inflammation of the skin that occurs in oval patches of variable size situated for the most part on the anterior surfaces of the lower extremities. These nodular lesions are elevated, hot, painful and covered by rose-red, shiny, smooth skin. The nodules appear in crops, last from a few days to several weeks and slowly disappear, going through the characteristic purple to yellow to green changes of an ordinary bruise.

Erythema nodosum is not a rare disease. It appears most commonly in young women, the highest incidence being in the spring months. It is sometimes recurrent and is usually preceded by mild constitutional symptoms such as fever, malaise and pain in the muscles and joints.

Many diseases are associated with this lesion and it has been described in association with sarcoidosis, tuberculosis, streptococcal infections, lymphogranuloma inguinale, secondary syphilis, coccidioidomycosis, non-specific hilar lymphadenopathy; indeed almost any infectious disease may produce the condition. It has also been associated with the ingestion of bromides, iodides and sulphonamides.

Several recent reviews have stressed these points,[1-3] while also bringing out the fact that the proportionate incidence of the causes listed above varies in different countries.

A patient was well until four weeks before admission to hospital when she developed generalized muscular aching, sore throat, a temperature of 102° F., and a mild headache. She took some A.P.C. and C. tablets and started to feel better after about three days. She was not forced to bed with this rather minor illness, and stated that she was back to normal in about one week. With the disappearance of her cold symptoms, she developed redness and swelling of an old appendectomy scar, which, within a day, became very tender and painful, and she noticed tender nodules in the scar itself. After four days' worsening of this complaint, she

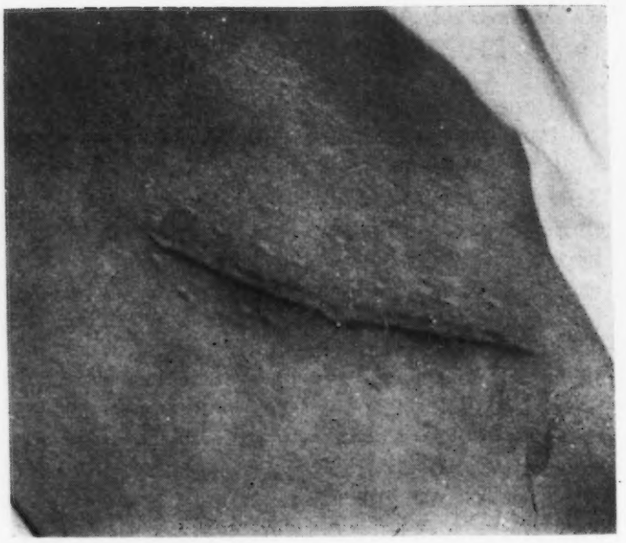

Fig. 1.—Photograph of appendectomy scar showing swelling and nodular inflammation.

went to a physician, who ordered 12 tablets of an novobiocin-tetracycline combination, which did not influence the painful scar.

One week before admission, the scar of a median nerve repair in her left upper arm became swollen and red, with tender nodules. Five days before admission red, tender nodules appeared in the anterior surface of the left leg and later in the right leg below the knees. The next day, the right knee became swollen and tender, and she was unable to walk because of the intense discomfort. No other joints were affected. She had no fever at this time.

At the time of admission to hospital, her complaints, then, were tenderness and pain in the scars as described; painful, tender nodules in the lower legs and a tender, swollen, painful, right knee.

She had had two previous attacks of swollen red areas in the lower legs, similar to the present illness, diagnosed as phlebitis by her family physician, in Glasgow, Scotland, in 1956, lasting about three months and disappearing spontaneously, and in 1954, another attack, lasting about four weeks. In these instances, there was no involvement of scar tissue or joints. Since the attack in 1956, she had noticed mild tenderness over both tibias when she exerted heavy pressure against them. However, their external appearance was normal.

She has had pain in the right lower quadrant of the abdomen intermittently for the past ten years, and this has been variously attributed to a cyst of the ovary and a spastic colon, but it did not worsen over the years.

Past operations include an uncomplicated appendectomy, performed in 1947, and dilatation and curettage for investigation of infertility in 1952. At the time of this latter procedure, sodium thiopental was injected into the median nerve in the antecubital area, and she subsequently developed weakness and numbness in the left hand. The median nerve was explored three weeks later and was resected. There was partial recovery of power, but residual numbness remained.

The patient was born and raised in Glasgow, Scotland, and after leaving school at age 14, worked as a butcher for three years, cutting up beef carcasses. She then took a job as a conductress on a street-car, until her marriage in 1946. In 1947 she emigrated to Canada,

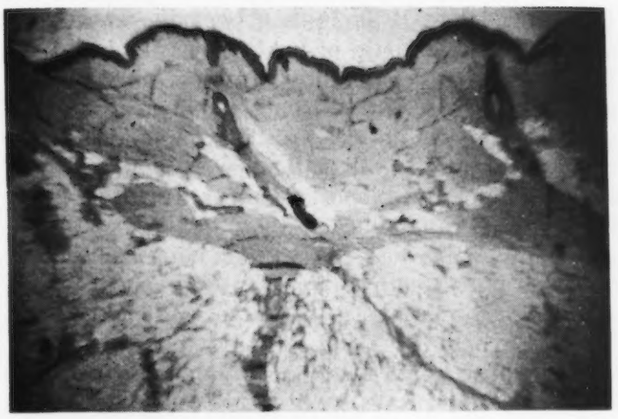

Fig. 2.—Low-power microphotograph of biopsy through nodule in the lower leg showing inflammatory changes in the fibrous strands separating the fat globules.

where she is taking care of her house and providing day care for children.

Her mother is alive and well, and the father, who has a duodenal ulcer, is also alive and well. There were seven siblings. One sister died of a spinal cord injury; the others are alive and well. There is no family history of rheumatic diseases or illnesses similar to the patient's, nor a family history of allergies. One younger brother had pulmonary tuberculosis in 1956, and was cured after one year in a sanatorium.

The patient took thyroid tablets, grain one daily, for obesity for four months before her illness, and this was supplemented during the month before her admission to hospital by dexedrine tablets 5 mg., three times a day. She has never taken a sulphonamide or penicillin, and there has been no recent ingestion of bromides or iodides.

Examination at time of admission revealed a rather obese, fair-skinned young woman who was in acute distress from painful legs which inhibited her from walking. Head and neck examination was negative apart from mild injection of the pharynx. The thyroid gland was normal. Chest was clear and no masses were palpable in the abdomen. The cardiovascular system was entirely normal, and the blood pressure was 130/80 mm. Hg. There was evidence of previous operation on the left median nerve. The rather widened scar in the left upper arm on the internal surface was tender and contained in its lower portion several red, raised, exquisitely tender nodules. There was mild weakness in the left hand, and diminished sensation to light touch and pin prick over the distribution of the median nerve in the left hand. In the right lower quadrant of the abdomen was a well-healed appendectomy scar which was red and elevated and tender to touch. In the depths of the appendectomy scar, several tender nodules were present which were exquisitely tender on even the lightest pressure. In the lower limbs, below both knees, were multiple raised red nodules, varying in size from about 5 mm. to 3 cm. These were on the anterior pretibial surfaces of the legs, and when they were close together were confluent. The posterior surfaces of the calves were normal and there was no evidence of phlebitis, the veins being normal. Homans' sign was negative.

In hospital, the urine was found to be normal, including the microscopic appearance and tests for bile and urobilin. The routine hæmogram showed a hæmoglobin value of 13.3 g., a white cell count of 7100, and a normal smear and differential count. The sedimentation rate was 80 mm. in one hour. Throat culture grew only *Streptococcus viridans* and *Staphylococcus albus* and was reported as showing no pathogens. A 24-hour culture of urine revealed no acid-fast organisms. Protein-bound iodine value was 4.4 mg. A chest radiograph was normal, as were the results of barium enema examination. The antistreptolysin "O" titre was 1:166. The Old Tuberculin test was negative.

From biopsy of the skin the upper layer of dermis showed some telangiectasia and the lower layer of dermis similar telangiectasia with a few lymphocytes surrounding these vessels. Most changes were confined to the underlying subcutaneous fat tissue, fibrous strands down from the dermis separating the subcutaneous fat into lobules. It showed infiltration by lymphocytes with some fibrosis, an occasional plasma cell, macrophage, and occasional eosinophilic leukocyte. It was the pathologist's opinion that this microscopic picture was compatible with erythema nodosum.

After the initial laboratory tests were made, the patient was given prednisone 10 mg. four times daily and acetylsalicylic acid 10 grains four times daily. The lesion cleared in a most dramatic fashion with use of this therapy. The red nodules on her legs faded into purplish areas in which the swelling diminished and finally, after the sixth day of therapy, disappeared. The nodules in the scar tissue were more resistant to treatment and required ten days of steroid therapy before they disappeared entirely. The sedimentation rate, on treatment, decreased to 20 mm. in one hour.

COMMENTS

In the case reported, the patient presented with the classical form of the disease. However, an additional finding was that of typical tender inflamed nodules in an appendectomy scar and in the scar from a median nerve repair in the left antecubital fossa. A search of the recent English-language literature and of leading text-books of dermatology has failed to reveal any description of erythema nodosum in scars. This feature must be an unusual, if not unique, occurrence.

SUMMARY

A case of erythema nodosum in a 33-year-old woman is reported. The patient had a rather typical form of the disease, but in addition had the unusual feature of involvement of scar tissue by the condition, the nature of which was confirmed by biopsy.

I wish to express my appreciation to Dr. B. Balshin, pathologist at The Doctor's Hospital, Toronto, who gave the pathological description of the biopsy and whose department prepared the illustrations.

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"RESISTANT" STAPHYLOCOCCI AND THE NEW SYNTHETIC PENICILLINS

WHILE infections due to penicillin-sensitive staphylococci have come under control through widespread use of antibiotics in recent years, the emergence of antibiotic-resistant strains has developed into a problem of major proportions. The staphylococcus menace is greatest in a hospital setting but is by no means confined thereto. Erythromycin, novobiocin and vancomycin proved initially effective against penicillin-resistant staphylococci but before they had been in use for long it became evident that staphylococci resistant to these newer antibiotics were flourishing. Furthermore, some of these drugs produced toxic effects, particularly upon the eighth cranial nerve. The development of additional antistaphylococcal agents without such disadvantages thus became a matter of no small importance.

In the early days of commercial production of penicillin it was discovered that several substances with antibiotic properties were recoverable from the fermentation products. Among these were penicillins F, K, X, and benzyl penicillin or penicillin G. The latter has stood the test of time as the most effective member of this group. Subsequently penicillin G was prepared in the form of various salts and esters with differing rates of absorption and grades of stability (e.g. procaine penicillin G and benzathine penicillin G). By treating the medium on which the penicillin was produced with certain chemical substances, additional penicillins have been evolved by a process of biosynthesis. One product prepared by this technique is phenoxymethyl penicillin or penicillin V, which is particularly stable in acid environments, is readily absorbed from the gastrointestinal tract and is admirably suited for oral administration.

In 1957 Batchelor *et al.*[1] isolated from mould fermentation products the basic molecule of all penicillins, 6-aminopenicillanic acid (6-APA), since referred to as the penicillin nucleus, a discovery first reported in 1959. It then became possible to modify the side chain of 6-APA by chemical synthesis with an apparently limitless number of moieties. Many of these synthetic penicillins possessed the power to kill resistant staphylococci in the test tube but most of them were inadequately absorbed into the blood stream or were too toxic for practical use. One of these earlier synthetic penicillins which was suitable for clinical application was phenoxyethyl penicillin or phenethicillin, subsequently marketed under the trade names of Broxil, Syncillin, Maxipen, Alpen, Chemipen, Dramacillin S, and Darcil. Early hopes that this product might prove to be more effectively absorbed, produce higher serum penicillin concentrations and provide greater antibacterial activity, particularly against staphylococci resistant to other penicillins, have not been borne out by recently reported studies,[2-4] and it appears that the major claims for the clinical superiority of phenethicillin over penicillins G and V are open to question.

The most recent fruits of 6-APA synthesis, however, offer considerable promise of superior effectiveness against staphylococci resistant to preexisting penicillins and other antibiotics. From Britain come enthusiastic reports concerning the properties of 6-(2,6 dimethoxybenzamido) penicillanate monohydrate, synthesized in the Beecham Research Laboratories and also known as BRL 1241 or Celbenin (Beecham).[5-11] In America, this antibiotic, designated as X 1497, is being manufactured by Bristol Laboratories and will soon be marketed under the trade name, Staphcillin.[12] These new synthetic penicillins have immunological characteristics and antibacterial activities distinct from penicillin G and other earlier penicillins.

BRL 1241 and X 1497 are unstable in acid media, are therefore unsuitable for oral administration, and must be given intravenously or intramuscularly in order to produce therapeutically effective penicillin blood levels. After parenteral administration they are rapidly absorbed, peak levels of their concentration in the blood being attained within the first hour after injection. The blood concentration required for therapeutic effectiveness against staphylococci is in the range of 2 to 6 μg. per ml. These levels are approximately 100 times greater than the effective blood concentrations of penicillin G, hence continued high blood levels must be maintained and relatively large, repeated doses of the new synthetic penicillins are necessary.

Observations to date indicate that intramuscular doses of one or two grams every four to six hours consistently maintain blood levels of BRL 1241 and X 1497 within the range of their antistaphylococcal effectiveness. These penicillins are rapidly eliminated, the greater proportion of an administered dose being excreted, unchanged, in the urine within a few hours after injection, most of the remainder being excreted in the bile. In the tissues, peak concentrations of X 1497 have been

demonstrated 15 to 30 minutes after intramuscular injection, followed by a gradual decrease over the next few hours. Excellent concentrations were present in the prostatic fluid; concentrations in the kidney, cord blood, peritoneal, pleural and knee joint fluids were about the same as those in the blood; no X 1497 was demonstrated in saliva, cerebrospinal fluid or stools. An appreciable blood-brain barrier to X 1497 has been reported by one group of investigators.

In large part, though not entirely, the problem of staphylococcal resistance to earlier penicillins is due to the fact that certain strains of the organism, including some virulent ones which endanger life, produce the enzyme penicillinase which destroys the penicillin before it can kill the bacteria. The new synthetic penicillins, BRL 1241 and X 1497, are therapeutically effective against these resistant strains of staphylococci because they are not destroyed or appreciably inactivated by penicillinase and retain their antibiotic power despite the presence of this enzyme. That there are other mechanisms of penicillin resistance besides that due to penicillinase, however, is implied by the fact that some strains of staphylococci which do not form penicillinase are still capable of resisting the bacteriostatic and bactericidal effect of penicillin. Therefore it is possible that there may be some forms of staphylococci whose resistance to penicillin apparently does not depend on a penicillinase mechanism and which may not be affected even by the new penicillinase-resistant synthetic penicillins. Nevertheless no evidence of resistance to BRL 1241 has been detected in tests on more than 1100 strains of staphylococci, the majority of which were resistant to penicillin G; nor have several hundred strains of this organism shown any evidence of resistance to X 1497. In short-term experiments and clinical trials to date, staphylococci have not acquired significant resistance *in vitro* or *in vivo* to BRL 1241. Whether this experience will be sustained in future remains to be seen.

Paradoxically, although they are not significantly inactivated by penicillinase, BRL 1241 and X 1497 vigorously stimulate the formation of this enzyme by staphylococci with which they are in contact.

As noted, intramuscular doses of one to two grams of these new synthetic penicillins every four to six hours consistently produce blood penicillin concentrations of 2 to 6 μg. per ml., at which levels they have strong bacteriostatic and bactericidal activity against staphylococci which are resistant to high concentrations of penicillin G, penicillin V and phenethicillin, as well as against staphylococci which are sensitive to the latter antibiotics. However, in common with several other synthetic derivatives of 6-aminopenicillanic acid, BRL 1241 and X 1497 have a narrower range of effectiveness and less intrinsic antibacterial activity against penicillin-sensitive staphylococci and other organisms than that of the "natural" penicillins. Their main indication at present, therefore, appears to be in the treatment of staphylococcal infections resistant to other antibiotics.

In tests performed to date, these new synthetic penicillins have produced highly satisfactory results, clinically and bacteriologically, in the treatment of staphylococcal soft tissue infections, boils, abscesses, infected burns, osteomyelitis, pneumonia, lung abscesses, empyema, septicemia, endocarditis, pyelonephritis and other urinary infections, bronchiectasis, meningitis, brain abscesses, and staphylococcal arthritis.

No serious or systemic toxic effects have been observed to date in association with their administration. Urticarial and other skin rashes have occurred in a few instances, although several patients sensitive to other penicillins showed no evidence of sensitivity to BRL 1241 or X 1497. Occasional febrile reactions have followed the intravenous injection of X 1497.

At this stage it would be rash to predict the future of these new synthetic penicillins. Much more clinical experience will be necessary before their potentialities and limitations can be assessed. Nevertheless, their discovery appears to be an important advance and there is some reason for optimism in the expectation that still better products may emerge from this avenue of research. Even at this stage it appears that these synthetic penicillins offer the treatment of choice for staphylococcal infections resistant to other antibiotics. For infections due to sensitive staphylococci, penicillins G and V remain the most effective therapeutic agents.

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THE TREATMENT OF ACUTE RHEUMATIC FEVER

THE PUBLICATION in this issue of the results of the five-year follow-up of the United Kingdom-U.S.A. co-operative clinical trials of ACTH, cortisone, and aspirin in acute rheumatic fever, and the excellent accompanying article by Dr. Keith of Toronto, will be welcomed by the physician faced with the responsibility for the actual management of the patient. The review by Keith should serve to dispel, or at least lessen, the intensity of the therapeutic fog which has surrounded

Canad. M. A. J.
Oct. 8, 1960, vol. 83

our present approach to the treatment of acute rheumatic fever.

Reports in the medical literature over the last few years have served to confuse the physician and have led to a multitude of therapeutic regimens, each with its own staunch and inflexible group of supporters. There has been no unanimity of opinion about the precise way in which penicillin, salicylates, or hormones should be used for the patient's benefit. The areas of disagreement involve dosage, duration of treatment, and the use of these admittedly valuable agents singly and in combination. The natural history of the disease, especially since the advent of penicillin, has been overlooked by many therapeutic enthusiasts, and Keith does well to call attention to the decline in severity of the disease and to the infrequency with which valvular heart disease later develops in those who have no evidence of carditis during the acute attack. Even the question of duration of rest has become controversial.

In the midst of the arguments which have raged between the hormone enthusiasts and the advocates of salicylate therapy, there has been a tendency to minimize or overlook the importance of penicillin in the treatment of the acute disease. Setting aside for the moment the waxing and waning in the severity of disease through the years, it is possible that the decline in severity of rheumatic fever may be due more to the intensive use of penicillin than to either adrenal steroids or salicylates. Mortimer and Rammelkamp[1] have recently reopened the question not only of the duration of active penicillin therapy but of the actual role played by the streptococcus in the development of carditis. A group of 49 patients with acute rheumatic fever and carditis were treated with large daily doses of penicillin for six weeks, while 48 controls received no penicillin. At the end of one year, 21% of the treated group and 52% of the controls showed evidence of valvular disease. The authors' conclusions imply either that the streptococci exert their triggering effect even after they have been eliminated from the throat, or that an actual bacterial valvulitis occurs. If the results of this provocative study are confirmed, the precise manner in which penicillin is used may be far more crucial in the treatment of acute rheumatic fever than either salicylates or steroids, or both. Keith has obtained similar results using a more moderate dose of penicillin sufficient to eliminate streptococci from the throat. In any event, this work has served to emphasize the great importance of intensive penicillin therapy in the acute phase of the disease.

The relative merits of salicylates as compared with steroids in controlling the acute disease and in determining the frequency of cardiac sequelæ have been argued in a large number of published articles. There are those who insist that steroid therapy is the most effective in preventing the development of permanent cardiac disease. They cannot understand the reluctance of others to accept what they consider is proof beyond clinical doubt.[2] Others are equally convinced that salicylates offer as much or more.

The 1955 United Kingdom-U.S.A. co-operative clinical trial study, and the more recently published 1959 combined study,[3] have attempted to resolve the dilemma. Both studies have made praiseworthy attempts to set up adequate controls in dealing with a disease that is teeming with variables. Both conclude that adrenal steroids have no special advantage over salicylates as far as the prevention of ultimate cardiac damage is concerned. In the combined study of 1955, drug dosages were often inadequate by present standards and were not related to the patient's age, weight or body surface. The five-year follow-up study published in this number of the Journal indicates that the original conclusions of the study group still hold.

In the more recent investigation[4] four patients selected by envelope method for the salicylate group were changed to the hormone group by three participating investigators because it was "decided that the acute symptoms of these critically ill patients might be controlled more effectively with steroids than with salicylates". In spite of this statement, only one investigator disagreed with the final conclusion that steroids had no special advantage over salicylates as far as prevention of ultimate cardiac damage was concerned. It has admittedly become more difficult in this day and age to treat a seriously ill rheumatic patient without steroids, even if such a patient is part of a carefully designed scientific study. One recalls the dilemma of Sinclair Lewis' Martin Arrowsmith.

Neither of the above studies considered the possible advantages of combining salicylate in full dosage with steroids in high dosage. Illingworth[5] has in his own clinic carried out what appears to be a well-controlled investigation, comparing no fewer than six different treatment plans, and has concluded that the combination of salicylate and steroid in high dosage is the most effective method. The smallness of numbers in each group is a weakness of this study which certainly merits more consideration than it has hitherto received.

Drug dosage continues to be a problem. Illingworth used blood salicylate levels to regulate aspirin dosage and set 30 to 40 mg. per 100 ml. as an ideal serum salicylate concentration. Keith suggests a dosage schedule of 1/3 to ½ grain per lb. body weight per day. The use of salicylates in high dosage constitutes a real risk to the child which should be borne in mind, particularly by those more accustomed to treating adults.

The optimum dosage of adrenal steroid is not known at present. The United Kingdom-U.S.A. clinical trial studies used doses that were not related to weight or surface area and were probably inadequate for the older patients. Some studies have claimed that large doses were more effective

than small ones, and although the evidence seems convincing, real proof is lacking.

The duration of treatment with salicylates or steroids, or a combination of the two, appears at present to depend upon reasonable evidence of the appearance of signs of inactivation of infection as judged by sleeping pulse, sedimentation rate, C-reactive protein, temperature, and improvement in the patient's general condition. The decision may rest finally upon an educated guess.

Even the subject of bed rest in the treatment of acute rheumatic fever is controversial. There are those who insist upon prolonged bed rest, up to as long as six months in many instances. Others deny the value of prolonged bed rest and urge early ambulation as being in the end more beneficial, both for mind and myocardium. There is little real scientific evidence to guide us in our decision.

How, then, does one treat a child with acute rheumatic fever and probable cardiac disease? With penicillin, salicylate, steroid and bed rest — how much, how long, all together or one at a time? Keith has furnished a very useful therapeutic plan designed for the management of a patient with acute rheumatic fever, including recommended dosage of aspirin, hormone, and penicillin. Whether hormone or salicylate or both should be used is left to the physician to decide for himself. Perhaps one might borrow a page from that incomparable medical evangelist, Dr. E. P. Joslin, and substituting rheumatic fever for diabetes proceed somewhat as follows: the acute rheumatic fever patient will fare best if he imagines himself in a chariot drawn by three sturdy horses — penicillin, salicylate, and steroid. He may arrive at his destination if his chariot is drawn by only two horses, or perhaps even only one, but he will have a rough journey and his arrival will be less certain. He should have a comfortable padded seat in his chariot to permit rest, but at some point in his journey, just where we are not sure, he would do well to get out of his chariot and jog along beside his horse, reins in hand.

H.M.

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ENDOMETRIAL CANCER

FOR some time there has been considerable doubt about the proper management of malignancies arising in the body of the uterus. The discrepancies in results of treatment appear to arise for several reasons. Aside from the extension of the primary lesion, the most important factors appear to be the histological group of malignancy and the duration of the lesion. Javert believes that there is an interval of almost 10 years between the time the lesion is instigated and the time when actual invasion occurs.

Evaluation of different methods of management inevitably revolves about the pivot of irradiation. No one denies that removal of the entire uterus with the adnexa is mandatory in all except the palliative procedures. The Wertheim type of hysterectomy has not been proved to offer any improvement in the prognosis.

The problem, then, is this: Should any or all patients with adenocarcinoma of the fundus receive irradiation? Should the irradiation be administered preoperatively or postoperatively?

Assuming that the lesion has not invaded the endocervix, it is probably preferable that the patient receive intracavitary radium six weeks before hysterectomy. The hazards of irradiation in expert hands are minimal; the surgical difficulties resulting from such radium treatment are inconsequential and seldom encountered.

In the older, poor-risk patient with a low-grade lesion it is efficacious to perform surgical procedures as soon as the diagnosis is certain. This is preceded by the usual suturing of the cervix and ligation of the fallopian tubes.

The advantages of postoperative irradiation are difficult to fathom.

W.F.B.

THE MASKING OF PERNICIOUS ANÆMIA BY VITAMIN PILLS CONTAINING FOLIC ACID

THE hazards of taking "vitamin pills" for anæmia of unknown origin or for some other ill-defined complaint are stressed by Ellison, who reports two cases of pernicious anæmia in which the diagnosis was obscured by ingestion of vitamin preparations containing folic acid (*J. A. M. A.*, 173: 240, 1960). He refers to six similar cases in recent literature and expresses the belief that there must be many such instances in which this disease has been unrecognized and unreported. It is well known that while folic acid produces an adequate hæmatological response in patients with pernicious anæmia, it not infrequently precipitates the development of neurological lesions.

A warning concerning the use of folic acid was issued as long ago as 1947 (Editorial, *New England J. Med.*, 237: 713, 1947), and it is surprising indeed that drug manufacturers have not heeded this warning. Ellison suggests that folic acid should be removed from all multivitamin and iron preparations, and dispensed in individual tablets for use only when specifically indicated. It may well be queried whether there is a need for the plethora of multivitamin preparations now on the market.

W.G.

Canad. M. A. J.
Oct. 8, 1960, vol. 83

LETTER TO THE EDITOR

LATE TOXÆMIA OF PREGNANCY

To the Editor:

The very fine review article on late toxæmia of pregnancy by Drs. MacFarlane and Townsend (83: 540, 1960) points out the value of diuretics and reserpine in the treatment of this disease. It might appear, too, that more stress should be laid on the care of the patient during the prehypertensive phase if this disease is to be controlled.

In our practice we have regarded a sudden gain in weight, and peripheral œdema, as evidence of toxæmia of pregnancy no matter how early in the pregnancy it was noticed. The general principles of management of toxæmia were observed, rest, hospitalization where necessary, diuretics and reserpine. Treatment was commenced as early as 16 weeks in many cases. These measures, with a small dose of diuretic, most often one tablet a week, will control the œdema. This small dose was all that was required right to term for many of our patients, some of whom had a history of severe toxæmia in previous pregnancies. The doses of diuretic were increased if necessary, to two tablets a week, or even to a tablet every second day. This was the highest dose we required to control œdema. Our best results were in multiparas with a history of hypertension and severe toxæmia in previous pregnancies; these patients often seemed to settle down on this regimen as the pregnancy advanced, and their blood pressure gave less trouble towards the end of the pregnancy than at the beginning. Although our total number of patients is not great, we have seen over the years enough cases to judge that there are great advantages to be realized by treating pregnant patients right from the time they show œdema. There must be something wrong if œdema is present, and treatment is definitely not harmful. We would like to believe that toxæmia of pregnancy is 100% preventable if it is treated early enough. If this is not possible immediately, it is a goal to be striven for. We are sure, however, that we have not seen one case approaching pre-eclampsia in over two years.

W. H. LEON, M.B. and
Mankota, Sask. E. G. POWELL, M.D.

Medical News in brief

MAXIMUM PERMISSIBLE RADIATION DOSES

Factors influencing maximal permissible doses of radiations were discussed in the 1960 Gordon Richards Memorial Lecture delivered by Robert S. Stone at the annual meeting of the Canadian Association of Radiologists (*J. Canad. A. Radiol.*, 11: 26, 1960). The plural term "doses" is used in the title because there are different maximum permissible doses for total body exposure, exposure of the extremities and of the separate organs, and for various groups in the community.

For very low doses, genetic mutations are the greatest hazard. If exposure of the population at large is limited, it is possible to permit larger doses to occupational workers without greatly raising the rate of mutation in the germ plasm of any given population.

The International Commission on Radiological Protection, of which Dr. Stone is a member, has set up five population categories consisting of occupational radiation workers, adults who work in the vicinity of a controlled area, adults who enter a radiation controlled area occasionally, members of the public living in a neighbourhood of a controlled area, and the population at large. The most important group is the public living in the neighbourhood of a controlled area, as it contains children and pregnant women whose offspring will be irradiated from conception throughout life. For these a maximum permissible dose of 0.5 rem per year is set, as compared with 5.0 rem per year for occupational workers.

Three general radiation effects have important bearings on the problem of permissible doses. Firstly, life shortening; the author considers that there is a threshold dose above which irradiation does lead to life shortening, though the exact level of this dose is not known. Secondly, leukæmia induction; opinions appear to differ as to whether or not there is a threshold for leukæmia production, but in the author's opinion there is. Thirdly, genetic effects; much more information is needed before we can establish the presence or absence of a threshold level for these. There is still considerable uncertainty as to what dose of radiation is going to produce too heavy a burden of mutations for the human race to stand. It is the author's opinion that we should assume that there is no threshold for genetic effects and therefore should keep gonadal exposure very low.

The International Commission on Radiological Protection has made recommendations with regard to maximum permissible doses in almost all circumstances except in the field of medical radiology. In this field it is their opinion that the doctor himself should balance the good against any possible harm. They therefore place upon the medical profession the onus of decisions regarding the medical use of ionizing radiation.

In discussing chest x-ray exposures, an interesting point for comparison is quoted from the Adrian Committee report: "From natural sources the annual dose received by an individual would increase by about 20 mr. on going from a stone house in a limestone district to a granite house in a granite area (local gamma-ray increment), or going from sea level to live at an altitude of 5500 ft. (cosmic ray increment)." It is also noted that the difference between living in a wooden house compared with a brick house in Sweden is 55 mr. per year. These doses are contrasted with a single exposure dose in mass miniature chest radiography of 0.12 mr. ovarian for females, or mean testicular of 0.7 mr. for males, and also with the average female gonadal dose associated with a conventional postero-anterior chest film of about 0.2 mr.

The question of sensitivity of the embryo and fetus is discussed in relationship to radiological examinations during pregnancy. The author notes Hammer-Jacobsen's belief that radiological examinations should not be performed during the first four months of pregnancy, and his suggestion that in fertile women radiological examinations of the abdomen should be carried out only during the first 10 days after a regular menstrual period of normal intensity and duration. The author himself believes that some such rule will become routine in radiology departments even though many may mildly ridicule it today.

It is pointed out that in medical radiology, as in occupational exposure, we have entered the era when we must balance the risks against the advantages. The author concludes that the total medical radiation hazard has been overestimated, but because there are hazards, it is incumbent on radiologists to take all known precautions to keep the exposure of the gonads to the lowest possible level consistent with the medical needs of the patient.

THE ROLE OF TOTAL-BODY IRRADIATION IN THE DAWN OF THE HOMOGRAFT ERA

The administration of total-body radiation as a prelude to the transplantation of tissues between genetically unrelated individuals has recently been evaluated by Dealy (*Radiology*, 75: 11, 1960).

Potentially lethal doses of radiation may be employed in the expectation that infused bone marrow, by its functional replacement of the recipient's marrow, will provide effective support through the course of the acute radiation syndrome. This successfully grafted marrow should then be tolerant of other tissues grafted from the same or genetically identical donors. Alternatively, if there is an analogy between the suppressive effect of total-body irradiation on lymphopoietic and reticuloendothelial elements, and the perinatal state of immunologic immaturity, there may be hope that similar factors will operate during the post-irradiation period.

Of six patients comprising Dealy's experience in man to date, one survived 10 months up to the time of reporting, following the grafting of a dizygotic twin brother's kidney, combined with total-body irradiation.

It is stated that the use of total-body irradiation in the transplantation field has raised more questions than it has answered; the basic question of whether tolerance to homologous organs in the human can be induced by sublethal irradiation must be left open. The problems of guiding already desperately ill patients through the post-irradiation course are also many and varied.

Nevertheless, there would appear to be a reasonable foundation for the belief that ionizing radiation will play a major role in progress in the homologous transfer of whole organs.

TREATMENT OF DIABETIC GANGRENE

In the treatment of diabetic gangrene several factors must be considered. The disordered state of "diabetic" metabolism must be optimally adjusted in so far as possible, infection must be sought and treated, and a decision must be made as to whether the gangrenous lesion is to be treated by conservative or surgical means. In discussing these various aspects of treatment, Strauzenberg of Dresden, East Germany (*Deutsche Gesundhwes.*, 15: 935, 1960) reports 203 cases of diabetic gangrene observed between 1927 and 1950. In this group 66% were treated conservatively. In addition to the usual measures, Strauzenberg describes the use of intra-arterial infusions of acetylcholine as an added therapeutic procedure. He begins with 200 mg. of acetylcholine in 200 ml. of Ringer's solution and increases this gradually to 500-600 mg., the total amount being infused within 40 to 60 minutes. He usually administers this infusion two to three times a week. Subcutaneous insufflation of oxygen in the area of gangrene was also stated to be effective in relieving pain as well as in combating the underlying disease process. Other agents, administered by intra-arterial infusion with claimed beneficial effects, were nicotinic acid derivatives and preparations of adenylic acid. Whilst Hdyergine, Priscoline and other sympatholytics increase the circulation in the skin, some of the derivatives of adrenaline have a special effect on the circulation in muscles and improve exercise tolerance in intermittent claudication.

TREATMENT OF TOXIC NODULAR GOITRE WITH RADIOACTIVE IODINE

In a total series of 1603 hyperthyroid patients, 436 patients with toxic nodular goitre were treated by Eller *et al.* (*Ann. Int. Med.*, 52: 976, 1960) with I^{131}; the toxic nodular group included 127 patients with solitary nodules. One-third of the treated patients were below the age of 40; three-quarters of them were female. The patients with toxic nodular goitre were considerably older than those with toxic diffuse goitre. Of the patients with toxic nodular goitre 92% were cured with radioactive iodine, and 8% were made permanently myxœdematous; the percentages were identical for toxic diffuse goitre. About 40% of the nodular and 50% of the diffuse toxic thyroid patients were cured with a single dose of I^{131}. The patients with Graves' disease averaged 1.9 treatments each, while those with toxic nodular goitres averaged 2.2 treatments each. Patients with toxic nodular goitres required an average total administered dose of 10.3 mc. of I^{131} to cause a remission in the hyperthyroidism; those with Graves' disease needed 7.2 mc. This represents the differences in uptake and size of gland, rather than radiosensitivity.

Solitary nodules in patients with hyperthyroidism respond well to treatment with radioactive iodine. Substernal thyroids, even very large ones, may be treated successfully with radioiodine; pressure symptoms due to goitre are not a contraindication to I^{131} therapy. All of this series of thyrotoxic patients had their hyperthyroidism controlled with radioactive iodine alone. The toxic nodular goitres averaged 53 g. in weight before treatment and 37 g. after treatment. The ability of a toxic nodular goitre to pick up radioactive iodine is only moderately less than that of a toxic diffuse goitre. Thirty-two per cent of the patients with Graves' disease and 18% of those with toxic nodular goitres showed some degree of exophthalmos. After treatment with radioactive iodine, eye signs improved but did not disappear, regardless of the type of thyroid gland the patient had.

Eighty per cent of all patients had pulse rates in excess of 100 per minute before treatment; treating the hyperthyroidism with I^{131} relieved almost all of the tachycardias. Atrial fibrillation was found in 25% of the toxic nodular goitres and in 10% of those with Graves' disease; after I^{131} therapy, one-half to three-quarters of the fibrillators reverted to a regular rhythm. Before treatment with I^{131}, one-quarter of the patients with toxic nodular goitres had some degree of congestive heart failure, as did 10% of those with Graves' disease; after therapy, there was marked improvement in the decompensated patients. Angina pectoris also improved after I^{131} therapy. Diabetes mellitus associated with hyperthyroidism lessened in severity when the hyperthyroidism was relieved with I^{131}.

(Continued on advertising page 29)

Canad. M. A. J.
Oct. 8, 1960, vol. 83

ASSOCIATION NOTES

AMBULANCE DRIVERS

The report of the Committee on the Medical Aspects of Traffic Accidents (*Canad. M. A. J.*, 83: 506, 1960) noted among other matters the importance of ambulance drivers themselves obeying traffic regulations, and the precarious economic state of many private operators. The Executive Committee proposed and the General Council adopted an addendum to the report recommending that ambulance drivers be instructed in first aid and the transportation of unconscious patients, and that when their economic situation is alleviated, they be required to carry adequate equipment, including aspiration apparatus. In view of this, it is interesting to learn from Dr. C. H. Andrews of Prince Albert that an advanced first aid course for ambulance drivers and attendants was held at the University Hospital, Saskatoon, in May 1960. Such courses were inaugurated by the Saskatchewan Division's Committee on Traffic Accidents and they have been adopted as a useful endeavour by the Division of Occupational Health of Saskatchewan's Department of Public Health. All ambulance personnel in the province are required to take the certificate of the St. John Ambulance and they must refresh their knowledge by attending one of these advanced courses every three years. The syllabus of the Saskatoon course anticipates the recommendations of the General Council by stressing the early care of head and spinal cord injuries and by teaching resuscitation, oxygen therapy and the use of suction equipment. Dr. Andrews remarks that he hopes that the Saskatchewan experience will serve "as a prod and encouragement to other areas".

PUBLIC HEALTH

SURVEILLANCE REPORTS OF EPIDEMIC OR UNUSUAL COMMUNICABLE DISEASES

PARALYTIC POLIOMYELITIS

Canada

During the 33rd week ending August 20, 1960, a total of 33 cases of paralytic poliomyelitis were reported to the Epidemiology Division. Thirty-four cases were reported in the 32nd week.

The current weekly totals are well below those registered at this time in the high-incidence years and the 1960 cumulative total to date is now one of the lowest for the comparable 33 weeks during the epidemic years since 1949.

Year	*1949*	*1951*	*1952*	*1953*	*1954*	*1959*	*1960*
Week 32	92	82	93	256	53	103	34
Week 33	128	82	71	268	55	107	33
Cumulative total to week 33	499	315	369	1143	379	667	320

Newfoundland

The great majority of cases have occurred this year on the west coast, where during last year's epidemic comparatively few cases were reported. This year the cases have been more sporadic, with no high concentration in any one particular area. Twenty-nine cases have occurred. There have been two deaths, in a 3-year- old boy and a 9-month-old boy. One had received three doses of vaccine and the other two doses. One case occurred in a 28-year-old expectant mother who had received three doses of vaccine; a miscarriage occurred in the second month of pregnancy. All isolations so far have been of poliovirus Type 1, as in last year's epidemic.

The table below shows the age group distribution and vaccination status for 28 cases:

	Total cases	*Doses* 0	1	2	3	N/K
0 - 4	18	6	3	5	3	1
5 - 9	6	1	1	1	3	—
10 - 19	3	2	1	—	—	—
20+	1	—	—	—	1	—
Total	28	9	5	6	7	1

British Columbia

To August 11, 94 cases of paralytic poliomyelitis were reported in British Columbia. The majority were concentrated in the Cariboo Health Unit, the bulk of the cases occurring in Prince George and environs. There was an earlier epidemic in this Health Unit, in the Burns Lake area where 23 cases were reported between January and April. The cases in Prince George started to appear towards the middle of June. To date, 19 have been reported from that vicinity and another one from Burns Lake.

So far over half of the cases have occurred within the Cariboo Health Unit, the remainder being scattered over the province. (In 1959, a total of 20 cases of paralytic poliomyelitis were reported in the Cariboo Health Unit, an attack rate of 31.2 per 100,000 population.) Fifteen cases have been reported on Vancouver Island, nine of which occurred in the Central Vancouver Island Health Unit.

Of the 94 cases reported, 26 patients were fully vaccinated (27.6%).

EPIDEMIC PLEURODYNIA (BORNHOLM DISEASE)

Since the end of July, 50 to 60 cases of epidemic myalgia have been reported in the Quesnel and Prince George areas of British Columbia. The clinical picture is typical, with fever, acute muscular pains and tenderness in the chest and/or abdomen. It is highly infectious, whole families being affected in communities. Relapses are frequent, and occasionally the aseptic meningitis syndrome is associated. Virus studies are under way. It is assumed that the outbreak is due to Coxsackie B5.

Some three to five hundred cases of epidemic pleurodynia have been reported in the Upper Fraser Health Unit area since the end of July. The symptoms are: malaise, fever up to 104° F., and chest or abdominal pains, often severe. Some patients are also suffering from headache and stiff neck, nausea and vomiting, suggesting aseptic meningitis.

RABIES (BAT)

A 29-year-old man dismantling a sign on top of a clock tower in Vancouver was bitten by a bat on the left little finger. This lone bat had been observed by the crew for the previous five days. The bat was killed on the following morning and direct examination of smears revealed the presence of Negri bodies. The patient is now receiving antirabies vaccine.

HUMAN RABIES

United States

A case of rabies has occurred in a nine-year-old boy in Atlanta, Georgia. The patient was one of seven children and one adult bitten by one of two dogs running amuck in the city on March 24, 1960. The boy was severely bitten on

PARALYTIC POLIOMYELITIS IN CANADA*
33RD WEEK—ENDING AUGUST 20, 1960

	Reported cases									Deaths		
	This week			Last week			To this week			To this date		
	1960	1959	1958	1960	1959	1958	1960	1959	1958	1960	1959	1958
Canada	33	132	9	34	132	9	320	667	64	28	59	6
Newfoundland	3†	10	—	3†	7	—	29	60	3	2	4	—
Prince Edward Island	—	1	—	—	—	—	1	1	—	—	—	—
Nova Scotia	2	1	—	—	—	—	7	2	—	1	—	—
New Brunswick	3	—	—	2	1	—	20	8	1	1	1	1
Quebec	2	100	3	10	110	—	60	493	15	9	42	—
Ontario	3†	6	—	1†	6	—	8	42	5	—	4	3
Manitoba	2	3	5	—	1	7	6	11	21	1	—	—
Saskatchewan	3	3	—	5	1	—	24	14	—	3	1	—
Alberta	5	3	1	4	4	2	54	15	10	2	1	—
British Columbia	10	5	—	9	2	—	110	10	9	9	2	2
Yukon	—	—	—	—	—	—	—	—	—	—	—	—
Northwest Territories	—	—	—	—	—	—	1	11	—	—	4	—

*Weekly returns based on telegraphic reports by provinces.
†Delayed reports.

the lip, nose, left elbow and lower back. A few hours after exposure he was given 2000 units of antirabic hyperimmune serum, and the day following he was started on anti-rabies vaccine. The dog, identified by the parents of the boy as the biting animal, was confined for about two weeks in a dog pound. The dog remained normal during this time and then was destroyed. Because of the normal behaviour of the dog, vaccination was discontinued after the seventh dose.

Initial symptoms were first noted on May 19 and death occurred two days later. At autopsy the brain was found to be Negri-positive, and the diagnosis of rabies was confirmed by mouse inoculation. The fluorescent antibody test was also found to be positive for rabies. It is stated that there obviously had been confusion in the identification of the biting animal by the parents and children.

This is the first reported case of human rabies for the United States in 1960. Three cases were reported for the same period in 1959.

Q FEVER

Twenty-five clinically and serologically proved cases of Q fever have been reported in Idaho in the past six months. The disease appears to be endemic in the south-central and the eastern parts of the State. In those cases for which animal contact has been established, sheep are the primary source of infection.

BOTULISM

Indian and Northern Health Services

On July 30 or 31, a quantity of spoiled seal meat was eaten raw in two small neighbouring camps near Lake Harbour, N.W.T. Twenty-four hours after the ingestion of the spoiled meat, a 20-year-old woman became severely and acutely ill. Her symptoms consisted of intractable vomiting and abdominal cramps, visual disturbances and generalized and increasing paralysis. Within about 20 hours of the onset of illness, the patient was dead, probably as a result of respiratory paralysis. After the death of this woman, Mr. Hughes, a teacher at Lake Harbour, destroyed all of the meat which was available in the two camps.

On the following day, August 2, two additional cases occurred, presenting the same symptoms, with definite paralysis of cranial nerves seven, eleven and twelve and with increasing paresis of limbs. By the evening of August 2, these two patients, one a middle-aged woman and the other a man about 30 years old, were still alive, but in serious condition because of inadequate respiration. Both patients were still alive on August 4 but it was not expected that either would survive.

Samples of vomitus were sent for analysis, since the suspected meat was not available for investigation. Although laboratory confirmation is not yet available, botulism is the most likely diagnosis.

LEPROSY

One case of leprosy has been reported from Calgary, Alta., for the week ending August 13, 1960. The patient is a 26-year-old man.

TETANUS

One case of tetanus has been reported from York County, New Brunswick, in a 26-year-old man. A case has also been reported in the province of Quebec for the week ending August 6, 1960.

Epidemiology Division, Department of
National Health and Welfare.

Ottawa, August 27, 1960.

BOOK REVIEWS

NONPENETRATING INJURIES OF THE ABDOMEN. R. H. Kennedy, Consulting Surgeon, Beekman-Downtown, Bellevue and University Hospitals, New York. Edited by L. R. Dragstedt. 121 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $5.25.

This volume is written about a particularly important subject in these days of high-speed automobiles with several hundred fatalities over every holiday weekend. It is undoubtedly a useful reference book, but not a particularly readable one. It is distinguished by a complete absence of tables, illustrations or diagrams or other *aids memoire* which this reader finds helpful. There are a few statements in the book which are open to question, e.g. that on abdominal paracentesis (page 21) describing the technique of introducing a polyethylene catheter through a No. 13 needle: "There is no possible danger of bowel injury with the polyethylene catheter . . ." is a dogmatic statement which is hard to accept. There have been and will be complications from abdominal paracentesis which must be admitted. Undoubtedly it is still a useful procedure provided some reservations are kept in mind.

The particular value of the book to this reviewer is the fact that this is a subject which is inadequately covered in textbooks and there are very few monographs or articles which attempt to discuss it as fully as Dr. Kennedy does. For this reason it is a very useful addition to medical literature.

Canad. M. A. J.
Oct. 8, 1960, vol. 83

BIOMECHANICS OF THE CENTRAL NERVOUS SYSTEM: SOME BASIC NORMAL AND PATHOLOGIC PHENOMENA. Alf Breig. 183 pp. Illust. The Year Book Publishers, Inc., Chicago, Ill., 1960. $8.50.

This important work comes from the Institute of Anatomy, University of Uppsala, and the Department of Neurosurgery, South Stockholm Hospital.

Dr. Breig has analyzed, in detail, the anatomical changes which occur in the brain-stem, spinal cord, meninges and peripheral nerves in the normal movement from full extension to full flexion of the head and vertebral column of 143 human adults examined at autopsy. The maximum relaxation of all these structures is present in full extension, and tension on them is increased as the head and vertebral column are flexed.

The author's observations show that these increased tensile changes in the posterior cranial fossa and vertebral canal do not cause any upward movement of the spinal cord within the limits of normal flexion.

In extension, the relaxation of the intravertebral tissues allows adjacent segments of the spinal cord to be pressed together. This is most dramatically shown in histological sections of spinal cords which have been fixed when the head and spine were fully extended. The longitudinally running intraspinal nerve fibres show their "relaxation" by the waviness of their course. The cross-sectional area of the spinal cord is increased in this extended (relaxed) position. The movement of flexion causes a straightening out of the nerve fibres and a diminution in the cross-sectional area of the spinal cord.

The book is beautifully illustrated and well produced. It is a valuable addition to the library of anyone interested in the neurological sciences.

THE CHEMICAL SENSES IN HEALTH AND DISEASE. H. Kalmus, Reader in Biology, University of London, and S. J. Hubbard, Lecturer in Physiology, University College, London. 95 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto.

Dr. Kalmus and Dr. Hubbard have expanded an article on the chemical senses, which originally appeared in the *Scientific American*, into an interesting monograph which appears as publication No. 394 in the American Lecture Series. The authors emphasize the complex nature of taste and smell and the inadequacy of the present hypotheses of their mechanisms. After a brief review of the anatomy of the taste receptors and the behavioural and electrophysiological evidence of their function, a good deal of attention is paid to the genetical differences in ability to taste, particularly for the phenylthioureas. There is evidence that those who cannot taste these substances are slightly more prone to develop adenomatous goitre.

In the chapter on smell the chemical complexity of natural odours is emphasized; gas chromatographic analysis has now shown that geranium oil contains at least 100 separate volatile components. The bipolar nerve cells of the olfactory epithelium at the top of the nasal cavity, just under the piriform area and olfactory bulb, are thought to be the olfactory receptors. This epithelium covers a much greater area in many animals. The authors suggest that the number of classes of olfactory receptors is not very large but that each class comprises many thousands of like receptors, each responsive to vast numbers of compounds but to a variable degree; from the variable excitations to these receptors any particular olfactory sensation would then be centrally compounded. There is a brief discussion of Ottoson's work on the "electro-olfactogram" and his demonstration that an odour produces a slow negative potential in the olfactory epithelium; and of Adrian's investigations showing that this potential is maintained during stimulation, and thus adaptation to smell is probably largely central.

There is a relatively detailed discussion of the design of the investigation of taste and smell differences and preferences in human beings and of the various factors which may affect the accuracy and validity of such investigations. The chapter on chemical sensation in disease is very brief.

The authors conclude that "the chemical and physical properties of sapid or odorous substances can account only for some aspects of the chemical sensations—those concerned with the peripheral receptors, for example—and not for others which are based on more central neuronal organization."

This monograph gives the reader some orientation in the modern concepts of taste and smell. Its language is clear. Despite its brevity, one is left with the impression that more specific information could have been provided in the same space. There is a useful bibliography.

THYMECTOMY FOR MYASTHENIA GRAVIS. A Record of Experiences at the Massachusetts General Hospital. Henry R. Viets and Robert S. Schwab, Boston, Mass. 143 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $7.00.

The authors' experience with myasthenia gravis is worthy of consideration, since over 500 cases have been studied under their direction at the Massachusetts General Hospital since 1935. In this group, 139 thymectomies were performed. Many years of continued follow-up study at their myasthenia gravis clinic have provided an enormous amount of material for valid statistical studies of this rare disease, the treatment of which is still considered controversial by many.

This small book presenst a detailed history of the disease and a full description of its clinical aspects. The principles underlying choice of treatment are fully discussed by the authors. This constitutes highly recommended reading for the clinician not familiar with this rare disease before deciding on medical or surgical treatment for any individual patient.

To complete the review of present-day knowledge of this disease, four specialists have written on their experience in their own particular fields. Dr. Benjamin Castleman discusses the pathology of the disease and Dr. Lawrence L. Robbins its radiological features. Dr. Richard H. Sweet describes the technique of thymectomy, and Dr. James L. Vanderveen gives his experience with anæsthesia for thymectomy.

The final section of the book is devoted to an evaluation of the results of thymectomy by the two authors.

This book will prove of great value to physicians caring for patients with this disease and will provide useful reading material for anyone with an interest in this intriguing disorder.

MEDICAL NEWS *in brief*

(Continued from page 826)

IMMUNE MILK

In view of claims currently appearing in the lay press to the effect that a product manufactured under the name "Immune Milk" constitutes an effective form of treatment for rheumatoid and other forms of arthritis, the following statement has been issued by the Canadian Arthritis and Rheumatism Society: "According to the medical advisors of the Canadian Arthritis and Rheumatism Society, the claim advanced by Professor William E. Peterson, Specialist in Dairy Husbandry, University of Minnesota, that so-called 'Immune Milk' is beneficial in the treatment of rheumatoid arthritis is not supported by scientific evidence." The product known as "Immune Milk" is presently being manufactured and marketed to the public in areas of the United States. It is claimed that it contains streptococcal and staphylococcal antibodies which have been produced in the udders of cows injected with antigenic doses of these organisms. It is further claimed that patients with rheumatoid and other forms of arthritis will be benefited by drinking considerable quantities of milk produced by cattle treated in this way. Having regard to the welfare of many thousands of persons suffering from rheumatoid arthritis, the Canadian Arthritis and Rheumatism Society has stated its regrets that "Immune Milk" has been made known to the general public as a form of treatment for this disease, before its therapeutic value has been assessed and scientifically proved or disproved. The generally accepted status of this product is summed up in the statement of the Medical Director, Arthritis and Rheumatism Foundation of the United States, as follows: "In short 'Immune Milk' is, unfortunately, just the latest of hundreds of misrepresented products claiming to cure or relieve rheumatoid arthritis."

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RECENT AND FUTURE MORTALITY TRENDS

The mortality in the general population of the United States has shown a marked decrease in the past 20 years. Among whites, this decrease was greatest from 1943 to 1950, with relatively slight improvement during the 1950's. In the non-white population the decreasing trend was rapid and continuous throughout the past two decades, but the death rate in non-whites is still several times that of whites in the 15 to 74 year age group. The decrease in mortality has been more rapid among females so that the sex difference in mortality has become more marked, especially among white persons. Whatever the forces responsible for the decreasing trend, they appear to have had a greater effect on the lower socio-economic classes than on the middle or upper socio-economic groups. Between 1930 and 1950, the disparity in death rates between professional and managerial occupations on the one hand, and semi-skilled workers on the other, narrowed appreciably. The previously more favourable mortality rate of agricultural workers as compared with other occupational groups is also becoming less pronounced.

While the future trend is a matter of conjecture, it appears obvious that some of the major causes of the long-term mortality decrease have run their course. Though further reduction in death rates from communicable diseases, tuberculosis and influenza may occur, they will not affect the total mortality figures appreciably. Nor will improvements in standards of living be as great a factor as in the past. Solution of some public health problems may create new ones, as exemplified by the development of resistant strains of organisms after the introduction of antibiotics. Additional unfavourable influences may be created by added physical and emotional hazards of city life, increased air pollution, exposure to a growing variety of chemical agents, greater abundancy of "rich foods" and the unknown long-range effects of atomic energy.

The mortality experience of the past 50 years cannot be taken as a reliable guide to the future, since subsequent reductions will depend largely on the trend of death rates due to cardiac and malignant diseases. It is likely that such changes in mortality as do occur will be of a different character from those of the past two decades. In addition to the increasing number of new hazards, there is likely to be an adverse effect on mortality in the older age groups associated with the fact that greater numbers of persons with serious ailments such as diabetes have their life prolonged to a greater degree than in the past.

Nevertheless there is good cause for optimism regarding the future. Mortality rates throughout Western Europe and North America have been declining for over a hundred years; facilities for control and cure of a large number of diseases are greater than ever before; and an increasing volume of potentially fruitful research is being conducted in the fields of heart disease, cancer and other major causes of death.—*Statistical Bulletin*, Metropolitan Life Insurance Company, Vol. 41, June 1960.

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SILASTIC PATCH PROSTHESIS FOR CENTRAL PERFORATIONS OF THE EAR DRUM

Preliminary observations hold promise that the use of prosthetic patches prepared from silastic, a semi-transparent film manufactured by the Dow Corning Corporation,

(Continued on page 31)

MEDICAL NEWS *in brief*

(Continued from page 29)

may be of value in effecting closure of central perforations of the tympanic membrane. This material is easily manipulated and non-irritating to tissues when properly prepared and sterilized by autoclaving. The patch is held in place by a silicone adhesive containing 6% glacial acetic acid which stimulates epithelial growth, in some cases leading to healing of the perforation. To date this procedure has been applied only to central perforations in the presence of a normally functioning Eustachian tube and a dry, non-infected middle ear. If there is no disruption or fixation of the ossicular chain, impaired hearing is usually restored by such temporary closure of the perforation. If this is the case, the edges of the perforation are cauterized and covered by another silastic patch fixed in place by silicone adhesive. Perforations tend to become progressively smaller as fresh patches are applied every four to six weeks. Further observations will be required before this procedure can be evaluated more definitely.

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INDUSTRIAL HYGIENE FOUNDATION OF AMERICA, INC.

The 25th Annual Meeting of the Industrial Hygiene Foundation of America, Inc., will be held at the Mellon Institute, Pittsburgh, Pa., on October 26 and 27. The program for this Silver Anniversary meeting will consist of Management Conferences on Wednesday, October 26, and Sectional Conferences on Thursday, October 27, in the medical, legal, engineering, and chemical-toxicological fields.

Each person planning to attend the meeting is requested to fill out an advance registration card and return it to the Industrial Hygiene Foundation, 4400 Fifth Avenue, Pittsburgh 13, Pa. No admission cards will be sent. Badges will be held for registrants at the registration desk in the Mellon Institute.

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VIRAL NEPHRITIS

Until recently, the role of infection in the etiology of glomerulonephritis has been largely, though not entirely, limited to the concept of a sensitivity reaction to products of streptococcal infection, with the kidney as the target organ. A group of clinicians, under the direction of Professor Michon of Nancy, France has recently described six cases of nephritis of viral origin reportedly confirmed by serological studies (*Presse méd.*, 68: 309, 1960).

Clinically, their disease was characterized by an onset which either coincided with a viral infection, usually in the upper respiratory tract, or followed upon such infection after a brief interval. This was associated with hæmaturia and elevation of the blood non-protein nitrogen. Such viral nephritis could accompany atypical pneumonia, mumps, acute pericarditis, or infectious hepatitis, and at times was accompanied by diffuse neurological signs. Recovery usually occurred without sequelae, and no chronic involvement has been observed in the patients reported to date, after a follow-up of six to twelve months' duration. Thorough search for bac-

(Continued on page 34)

Canad. M. A. J.
Oct. 8, 1960, vol. 83

survey of survival in inoperable prostatic Ca.*

In their study of TACE in the treatment of carcinoma of the prostate, Carroll and Brennan conclude: "An 80-month survey of a group of 50 patients with prostatic cancer is reported. These patients were given TACE, a long-acting synthetic estrogen, in daily doses varying from 24 to 144 mg. for periods of time ranging from 24 to 80 months. Twenty-eight of the patients are still living at the time of this report and 22 have died. [Seventeen of the living patients have had orchiectomies in addition to TACE therapy.] Response to the drug has been generally gratifying, as evidenced by decreased pain, gain in weight, reduction of acid phosphatase levels, and regression of matastatic lesions. The medication has a long duration

of action, and it has proved valuable in the treatment of patients unimproved on therapy with other estrogens. Enlargement of the breasts occurred in about 80 per cent of the patients. Otherwise, TACE was well tolerated even in extremely high doses. The drug differs from other synthetic and natural estrogens in that it does not produce enlargement either of the adrenal or the pituitary glands. Moreover, TACE does not adversely affect the adrenal cortical function, nor does it cause gastrointestinal symptoms or oedema. Five-year survival rates with TACE are moderately higher than those reported for similar patients treated comparably with diethylstilbestrol."

MEDICAL NEWS *in brief*

(Continued from page 31)

terial infection failed to reveal any trace of streptococci, either by culture or antibody level determination. Leukopenia with lymphocytosis and monocytosis may be of value in raising a suspicion of this type of renal lesion. A weak and transiently positive blood Wassermann reaction, abnormal liver function tests, positive Paul-Bunnell reaction or the presence of cold agglutinins may be similarly interpreted. Positive identification of the virus involved may be facilitated by kidney biopsy. The pathogenesis of this disease is still undetermined; the main theories include direct invasion of the kidney by the virus, or a hypersensitivity reaction manifesting itself in renal tissue. The authors acknowledge the work of the Canadian investigators, J. K. Martin and R. Reed, in this field, and conclude with the statement that we are only on the threshold of great developments which recent clinical and technological refinements have permitted in our understanding of viral diseases. Confirmation of these concepts will be awaited with interest.

POSTGRADUATE REFRESHER COURSE—RHEUMATIC DISEASES

The Faculty of Medicine, Department of Medicine and Department of Surgery, of the University of Toronto, is offering a one-day postgraduate refresher course: "Current Concepts in Rheumatic Diseases" on Thursday, October 27, at Sunnybrook (D.V.A.) Hospital, Toronto.

Papers scheduled for the course, which carries six hours of Category 1 Study Credits, are: The Examination of the Musculo-Skeletal System, Dr. H. A. Smythe, Toronto; The Natural History of Marie-Strümpell Spondylitis, Dr. P. S. Rosen, Dr. D. C. Graham, Toronto; Radiological Changes in Marie-Strümpell Spondylitis—Dr. P. S. Rosen, Dr. H. A. Smythe, Dr. D. C. Graham, Toronto; Cardiac and Aortic Lesions of Marie-Strümpell Spondylitis, Dr. H. A. Smythe, Toronto; Arthritis Complicating Genital Infections, Dr. Denys K. Ford, Vancouver; The Treatment of Acute Rheumatic Fever, Dr. J. D. Keith, Toronto; The Collagen Diseases, Dr. M. A. Ogryzlo, Toronto; Recent Advances in the Clinical Aspects and Diagnostic Measures in Rheumatoid Arthritis, Dr. J. J. Bunim, Clinical Director, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland; The Treatment of Rheumatoid Arthritis, Dr. Wallace Graham, Toronto; The Team Approach to Therapy in Rheumatic Disease Centres, Dr. Norrie Swanson, Toronto; The Use of Splints, Dr. Norrie Swanson, Toronto; Anti-Malarials in the Treatment of Rheumatoid Arthritis, Dr. A. W. Bagnall, Vancouver; Surgery of Rheumatoid Arthritis of the Hip, Dr. D. L. MacIntosh, Toronto; Surgery of Rheumatoid Arthritis of the Hands, Dr. W. R. Harris, Toronto; Surgery of Rheumatoid Arthritis of the Feet, Dr. F. P. Dewar, Toronto; Surgery of Rheumatoid Arthritis of the Knee, Dr. Carroll A. Laurin, Montreal.

(Continued on page 38)

as it calms anxiety!

Smooth, balanced action lifts depression as it calms anxiety... rapidly and safely

Balances the mood – no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient *–they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation*–they often deepen depression.*

In contrast to such "seesaw" effects, Deprol's smooth, *balanced* action lifts depression as it calms anxiety–both at the same time.

Acts swiftly – the patient often feels better, sleeps better, within a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Acts safely – no danger of liver damage. Deprol does not produce liver damage, hypotension, psychotic reactions or changes in sexual function–frequently reported with other antidepressant drugs.

Bibliography *(13 clinical studies, 858 patients)*: **1.** Alexander, L. (35 patients): Chemotherapy of depression – Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. **2.** Bateman, J. C. and Carlton, H. N. (50 patients): Meprobamate and benactyzine hydrochloride (Deprol) as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy 6:648, Nov. 1959. **3.** Beerman, H. M. (44 patients): The treatment of depression with meprobamate and benactyzine hydrochloride. Western Med. 1:10, March 1960. **4.** Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. **5.** Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System 20:142, (Section Two), May 1959. **6.** Gordon, P. E. (50 patients): Deprol in the treatment of depression. Dis. Nerv. System 21:215, April 1960. **7.** Landman, M. E. (50 patients): Clinical trial of a new antidepressive agent. J. M. Soc. New Jersey. In press, 1960. **8.** McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression – New technics and therapy. Am. Pract. & Digest Treat. 10:1525, Sept. 1959. **9.** Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. **10.** Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. **11.** Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. **12.** Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy 7:28, Jan. 1960. **13.** Splitter, S. R. (84 patients): Treatment of the anxious patient in general practice. J. Clin. & Exper. Psychopath. In press, April-June 1960.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

▲Deprol▲

†TRADE-MARK

WALLACE LABORATORIES / *Toronto, Ontario*

MEDICAL NEWS *in brief*

(Continued from page 34)

SOVIET SCIENTIFIC PUBLICATIONS IN ENGLISH

The "Program For Scientific Translations in Israel" is an organization which was inaugurated for the purpose of providing English translations of important Russian books and articles of scientific interest. Material is selected for translation in accordance with the requirements of the National Science Foundation, Washington, D.C., which initiated this program and provides its support. "The Program for Scientific Translations in Israel" distributes all translations listed in its catalogue to areas outside the U.S.A.

The 1960 catalogue, which contains listings of translations of Russian works in the field of medicine, as well as of other sciences, may be obtained on request to: Program for Scientific Translations, P.O. Box 7145, Jerusalem, Israel.

SECURITE ROUTIERE

Tout conducteur de véhicule doit rester constamment maître de sa vitesse et mener avec prudence son véhicule, rappelle un porte-parole du Ministère provincial des Transports et Communications de la province de Québec.

Il ne suffit pas d'énoncer le précepte, il faut encore insister sur les modalités d'application, qui se résument à ceci:

1. Avoir une bonne connaissance des prescriptions du Code de la route.

2. Savoir que dans les agglomérations deux personnes sur trois tuées par l'automobile, sont des piétons; accidents qui peuvent être évités par une prudence accrue.

3. Prendre les précautions qu'imposent les circonstances, surtout

(a) lorsque les conditions de visibilité sont insuffisantes;
(b) dans les virages;
(c) sur les chemins en pente;
(d) aux intersections;
(e) aux passages à niveau;
(f) à l'approche du sommet des côtes.

De plus, le conducteur doit régler sa vitesse en fonction des difficultés de la circulation et des obstacles qui peuvent se présenter même sur une route qui lui apparaît libre.

Tout véhicule en mouvement est précédé d'une zone de danger, qui correspond à l'espace qu'il parcourt pendant le temps de réaction du conducteur, en plus du temps nécessaire au freinage.

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THIRD WORLD CONGRESS OF PSYCHIATRY

The Third World Congress of Psychiatry, Montreal, June 4-10, 1961, is being held at the invitation of McGill University and under the auspices of the Canadian Psychiatric Association. Meeting on the American continent for the first time, the Congress is expected to attract some 3000 delegates from 62 nations. Representatives will come from psychiatry and such allied fields as general medical practice, psychology, biochemistry, nursing, sociology, anthropology, social work, and pharmacology.

Copies of the Second Announcement, which carries information regarding program and registration, may be obtained by writing the General Secretary, III World Con-

(Continued on page 40)


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MEDICAL NEWS *in brief*

(Continued from page 38)

gress of Psychiatry, 1025 Pine Avenue West, Montreal 2, P.Q., Canada.

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UNIVERSITY OF TORONTO—POSTGRADUATE COURSE IN OTO-LARYNGOLOGY

On May 11, 12 and 13, 1961, a graduate course in oto-laryngology will be presented by the staff of the Department of Oto-laryngology, University of Toronto. They will be assisted by two distinguished guests: Dr. Philip E. Meltzer, Professor of Oto-laryngology, Harvard Medical School, and Chief of Oto-laryngology, Massachusetts Eye and Ear Infirmary; and Dr. W. G. Hemenway, Department of Oto-laryngology, University of Chicago.

The first session will begin on the afternoon of May 11, in the Royal York Hotel, Toronto, in association with the Section of Oto-laryngology of the Ontario Medical Association. The remainder of the sessions will be held in the clinical areas of the University of Toronto.

An attempt will be made to assess, discuss and demonstrate the newer procedures employed in the surgery of deafness. The present surgical treatment of head and neck problems will be presented, with special consideration of the new conceptions of the responsibilities of this specialty in their management.

The fee for the course will be $40.00 and will include a complimentary dinner.

Enquiries should be addressed to: The Director, Division of Postgraduate Medical Education, University of Toronto.

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SOCIETY OF NUCLEAR MEDICINE

At its 7th Annual Meeting, held in Estes Park, Colorado, in August, the Society of Nuclear Medicine elected the following officers: President, Titus C. Evans, Ph.D., Iowa City, Iowa; President-Elect, Lindon Seed, M.D., Chicago, Ill.; Vice President, Paul Meadows, M.D., Pittsburgh, Pa.; Vice President-Elect, J. R. Maxfield, Jr., M.D., Dallas, Texas; Secretary, Robert W. Lackey, M.D., Denver, Colo.; Treasurer, William H. Beirewaltes, M.D., Ann Arbor, Mich.; Historian, Asa Seeds, M.D., Vancouver, Wash. The following were elected as members of the Board of Trustees for three years: Clifford Allen, M.D., Portland, Ore.; Kenneth Moores, M.D., Seattle, Wash.; A. K. Atkinson, M.D., Great Falls, Montana; Samuel Nadler, M.D., New Orleans, La.; Jack Francis, B.S., Oak Ridge, Tenn.; George Hinman, Ph.D., Pittsburgh, Pa.; Marshall Rowan, M.D., Hawaii; Joseph Greenberg, M.D., New York, N.Y.; William Hutson, M.D., Chicago, Ill.; Monte Blau, Ph.D., Buffalo, N.Y.; and J. Kriss, M.D., Palo Alto, Cal.

The 8th Annual Meeting of the Society will be held at the Penn Sheraton Hotel, Pittsburgh, Pa., June 14-17, 1961. Further information from: The Administrator, Society of Nuclear Medicine, 430 N. Michigan Avenue, Chicago 11, Ill.

1960 MEETING: ASSOCIATION OF AMERICAN MEDICAL COLLEGES

Some 900 medical educators and guests from the United States and several foreign countries will attend the 71st annual meeting of the Association of American Medical Colleges, to be held October 30 - November 1 at the Diplomat Hotel in Hollywood Beach, Fla. Medical college costs, the use of private patients for educating the student, the functions and responsibilities of a university, and the doctor's responsibility in a changing world will all come under scrutiny during the three-day convention.

The $1000 Borden Award in the Medical Sciences and the Abraham Flexner Award for outstanding service to medical education will be presented Monday evening, October 31, at the Association's annual banquet with announcement of the recipient's names at the time of presentation. Dr. Joseph T. Wearn, recently retired Vice-President for Medical Affairs, Western Reserve University, will give the Alan Gregg Memorial Lecture.

The exhibit program, the first permitted at an A.A.M.C. annual meeting, will consist of educational exhibits from members of medical faculties and from publishing and pharmaceutical houses, and also exhibits from organizations whose objectives and programs are closely related to those of the A.A.M.C.

Preliminary programs have been sent to all members of the A.A.M.C. Interested persons may obtain this program, together with hotel registration cards, from Association headquarters, 2530 Ridge Ave., Evanston, Ill.

Hospital administrators and Deans participating in the Medical School-Teaching Hospital Section of the A.A.M.C. will arrive at the Diplomat October 28 in preparation for their two-day session, which will include discussions on "The Effect of Teaching and Research on the Medical School Hospital".

Changing patterns in medical practice and their effects on medical education will be deliberated at the Eighth A.A.M.C. Teaching Institute, to be held November 1-3 at Hollywood Beach.

88th ANNUAL MEETING, AMERICAN PUBLIC HEALTH ASSOCIATION

More than 5000 public health workers from the Americas and abroad will, it is anticipated, attend the 88th Annual Meeting of the American Public Health Association, to be held in San Francisco from October 31 to November 4. Among the principal topics are radiological health, health effects of food additives, and genetic and environmental aspects of public health. Several sessions will be devoted to a discussion of medical care programs and plans. On the morning of October 31, two simultaneous symposia will deal with man and his changing environment. In one, the changing cultural, sociological and political environment will be discussed; in the other, the changing physical, chemical and biological environment. Other general sessions will feature presentation of the highest

(Continued on page 42)

MEDICAL NEWS *in brief*
(Continued from page 41)

awards in public health: the Sedgwick Memorial Medal on the evening of November 1 and the Albert Lasker Awards of the American Public Health Association on November 3. The Association's President, Malcolm H. Merrill, M.D., Director of Public Health for the State of California, will address the general session on November 1. Sectional meetings will be held in the fields of Dental Health, Engineering and Sanitation, Epidemiology, Food and Nutrition, Health Officers, Laboratory, Maternal and Child Health, Medical Care, Mental Health, Occupational Health, Public Health Education, Public Health Nursing, School Health, and Statistics. Among the 60 related organizations holding sessions during the week will be the American Association of Medical Clinics, American Association of Public Health Physicians, American College of Preventive Medicine, Association of Schools of Public Health, American Society of Professional Biologists, and the Association of State and Territorial Health Officers.

Further information from: The American Public Health Association, 1790 Broadway, New York 19, N.Y.

A.M.A. POLICY ON HEALTH CARE FOR THE AGED

In June of this year, the American Medical Association through its President-Elect, Dr. Leonard W. Larson of Bismarck, North Dakota, urged the Republican Committee on Resolutions to adopt, as party policy, a plan for helping those of the aged who need help in the financing of their health care. The A.M.A., he said, was entirely in favour of helping those who need help, but did not believe that this necessitated the creation of massive federal machinery to help those who neither need nor want help, and who are capably handling their own problems at the present time. Dr. Larson pointed out that the majority of the aged are in good health, that relatively few of them are hardship cases, and that private citizens working at community level are already meeting a large proportion of their needs. Private health insurance and prepayment plans now enable most of the aged to finance their own health care under a wide diversity of plans. The A.M.A. stressed that the majority must be allowed to continue its use of the voluntary method without federal interference. To compel that majority to accept federal medicine rather than allow it to purchase its own medical care voluntarily, through its own resources, subverts the very principles upon which a free, democratic government must be based. The opinion was expressed that those who propose massive federal intervention in this field are, in effect, denying the right of individuals to pay voluntarily for their own health care and insisting that this right belongs to the federal government. Dr. Larson said that the nation's physicians are convinced that the health costs of the needy and near-needy can best

be determined locally, can best be administered locally, and can neither be determined nor administered adequately through mechanisms operating by remote control from Washington, D.C., of good medical care.

At the June meeting of the A.M.A. House of Delegates the following statement of policy was adopted by that body: "Personal medical care is primarily the responsibility of the individual. When he is unable to provide this care for himself, the responsibility should properly pass to his family, the community, the county, the State, and only when all of these fail, to the Federal Government, and then only in conjunction with the other levels of government in the above order. The determination of medical needs should be made by a physician and the determination of eligibility should be made at the local level with local administration and control. The principle of freedom of choice should be preserved. The use of tax funds under the above conditions to pay for such care, whether through the purchase of health insurance or by direct payment, provided local option is assured, is inherent in this concept. . . ."

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THE VAN METER PRIZE AWARD FOR 1961

The American Goiter Association, Inc., again offers the Van Meter Prize Award of $300 to the essayist submitting the best manuscript of original and unpublished work concerning "Goiter—especially its basic cause". The studies so submitted may relate to any aspect of the thyroid gland in all of its functions in health and disease. The Award will be made at the Annual Meeting of the Association in the Warwick Hotel, Philadelphia, Pennsylvania, May 3-6, 1961. A place on the program will be reserved for the winning essayist if he can attend the meeting. Where more than one author appears on the manuscript, they will be asked to designate a single recipient to receive the award.

The competing essays may cover either clinical or research investigations, should not exceed 3000 words in length and must be presented in English. Duplicate typewritten copies, double-spaced, should be sent to the Secretary, John C. McClintock, M.D., 702 Madison Avenue, Albany 8, New York, not later than January 1, 1961. Manuscripts that do not conform to these requirements will not receive consideration. The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

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NEW YORK PUBLISHER GRANTED RIGHTS TO SOVIET JOURNALS

A contract covering the translation into English of 23 major Soviet scientific journals has been renewed for 1960 and 1961 by representatives of Mezhdunarodnaya Kniga and Consultants Bureau Enterprises, Inc., a New York publishing house. The agreement guarantees Consultants Bureau exclusive English-translation rights for these journals in the fields of chemistry, physics, biology and medicine. The original arrangement was made between the two concerns in 1958 for one year only, and was the first such agreement

(Continued on page 44)

MEDICAL NEWS *in brief*

(Continued from page 43)

ever reached between an American publisher and the Soviet Union. The 1958 contract was renewed for one year in 1959.

Under the terms of the new two-year agreement, the Soviet agency facilitates advance receipt of Russian journals by the publisher here, and is pledged to use all means at its disposal to prevent infringement of the exclusive translation rights by any third party. Original art work and photographs appearing in the Russian periodicals are also rushed to the New York publisher by air mail. In return for these important advantages, Consultants Bureau is making what is described as a "reasonable royalty payment".

In addition, a special clause in the contract requires that Mezhdunarodnaya Kniga keep the publisher informed of any new scientific and technical journals to be published in the USSR. Such exchange of information is expected to improve communications between Soviet and Western scientists, since advance knowledge of important publications will make prompter translation possible.

Consultants Bureau pioneered the publication of translated Russian journals in 1949 with the *Journal of General Chemistry*, and is the world's largest producer of such translations—many of which are done under contract for American learned societies. The co-operation which has been established is already making possible the publication of cover-to-cover English translations of many of the journals within six months of their receipt from Moscow.

The journals covered in the agreement are: Biochemistry, Bulletin of Experimental Biology and Medicine, Proceedings of the Academy of Sciences of the USSR (Doklady), Journal of General Chemistry, Journal of Analytical Chemistry, Journal of Applied Chemistry, Bulletin of the Academy of Sciences—Chemistry Section, Automation and Remote Control, Colloid Journal, Metallurgist, Microbiology, Plant Physiology, Soviet Physics—Technical Physics, Soviet Physics—Acoustics, Pharmacology and Toxicology, Soviet Physics — Crystallography, Soviet Astronomy, Antibiotics, Instruments and Experimental Techniques, Entomological Review, Industrial Laboratory, Solid State Physics, Glass and Ceramics.

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AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The Part I Examinations (Written) will be held in various cities of the United States, Canada, and military centres outside the Continental United States on Friday, January 13, 1961.

Reopened candidates will be required to submit case reports for review 30 days after notification of eligibility. No reopened candidate may take the written examination unless the case abstracts have been received in the office of the Executive Secretary.

Current Bulletins outlining present requirements may be obtained from: Robert L. Faulkner, M.D., American Board of Obstetrics and Gynecology, 2105 Adelbert Road, Cleveland 6, Ohio.